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Archives of Physical Medicine and Rehabilitation

The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review --Manuscript Draft--

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Keywords:	spinal cord injuries; exercise therapy; metabolic diseases; cardiovascular diseases; biomarkers
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Abstract:	<p>Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI).</p> <p>Design Systematic review.</p> <p>Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (01/01/1970 to 31/07/2019).</p> <p>Eligibility criteria for selecting studies (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained \geq 1-year ago, (3) exercise intervention duration \geq 2 weeks, and (4) included any CMS risk factor as an outcome. The methodological quality of articles was assessed using the Downs and Black score.</p> <p>Results Sixty-five studies were included for the final analysis, including nine studies classified as high quality ($\geq 66\%$), 35 studies classified as fair quality (50-66%), and 21 studies classified as low quality ($< 50\%$). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper-body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES)-cycling. Improvements in lipid profile (4/5 studies) were observed following upper-body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES-hybrid, FES-rowing, and FES-RT.</p> <p>Conclusion Upper-body aerobic exercise training ($> 75\%$ maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.</p>

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5th March 2020

Dear Editor,

It gives us great pleasure to submit the following revised manuscript to *Archives of Physical Medicine and Rehabilitation*:

Title: The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

We would like to thank Reviewer 2 for their further helpful and insightful comments and hope that you will find our responses and associated amendments have improved the quality and presentation of this Systematic Review.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'J. Bilzon'.

Professor James Bilzon
Professor of Human and Applied Physiology

Dear Gerald Choon-Huat Koh (Section Editor, APMR)

We would like to submit a revised version of the manuscript entitled: **The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review** (Ref. No: ARCHIVES-PMR-D-19-01224R1). Please see our responses below, in green font, to the reviewer's comments, in black font. All changes made to the manuscript have been recorded using track changes.

We would like to thank the reviewers for their further comments.

Reviewers Comments and Author Responses

Reviewer 1:

I congratulate the authors for their work.

Thank you.

Reviewer 2:

The authors have tried to address the issues raised in this revision. However, the reason why hand searching was done on only two journals viz. Journal of SCM and the Archives of PM&R remains unclear, when there are other accepted "most common journals" around which may yield relevant articles such as the American Journal of PM&R, European Journal of P&RM, and Journal RM.

Thank you for your further comment on this issue. We will try to clarify our approach and reassure the reviewer. The initial electronic search, included ALL journals listed in the PubMed database. The second phase included a search of the reference lists of all identified articles and previous systematic reviews, to identify further articles from ALL journals. The third and final phase included a hand-search of the two specific journals which had returned the highest proportion of articles in the initial search. We believe this to be a very thorough approach and in keeping with best practice in Systematic Reviews. Of course, it is not possible to hand-search all journals and you will see from Line 162 that this process only revealed one additional study. I have changed the text to make this systematic approach more explicit, as follows (Lines 100-104):

“The reference list of included items and previous systematic reviews were checked and further articles identified. The final step involved hand-searching the journals which had returned the highest proportion of articles in the initial search, to identify any additional studies (e.g. Journal of Spinal Cord Medicine (1982-2018) and Archives of Physical Medicine and Rehabilitation (1985-2018)).”

The difference between hepatic insulin sensitivity (line 235) and peripheral insulin sensitivity (line 241) is still confusing, especially when related terms such as fasting insulin concentration, reduction in glucose and insulin, fasting glucose, fasting glycemic control keep appearing at various points (e.g. lines 236, 285, 334-8) - please clarify for the readers' benefit.

Thank you. For the benefit of the reader, we have included a new paragraph to explain these global terms (Lines 158-164):

“The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (e.g. oral glucose tolerance test) and categorized using indices such as ISI-matsuda.”

We have also inserted ISI-matsuda in to the list of abbreviations.

There is a small error in line 166: "reviewer's" should be "reviewers".

This has been corrected to “reviewers”.

Exercise and CMS risk in SCI

The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

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Conflict of Interest The authors declare no conflicts of interest

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Trial registration number CRD4201815110

The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

ABSTRACT

Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI).

Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (01/01/1970 to 31/07/2019).

Study Selection Articles were included if they met the following criteria: (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained \geq 1-year ago, (3) exercise intervention duration \geq 2 weeks, and (4) included any CMS risk factor as an outcome.

Data Extraction The methodological quality of articles was assessed using the Downs and Black score.

Data Synthesis Sixty-five studies were included for the final analysis, including nine studies classified as high quality ($\geq 66\%$), 35 studies classified as fair quality (50-66%), and 21 studies classified as low quality ($< 50\%$). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper-body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES)-cycling. Improvements in lipid profile (4/5 studies) were observed following upper-body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES-hybrid, FES-rowing, and FES-RT.

Conclusions Upper-body aerobic exercise training (>75% maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.

Key Words spinal cord injuries, exercise therapy, metabolic diseases

Abbreviations

CMS cardiometabolic syndrome

DBP diastolic blood pressure

ES effect size

FES functional electrical stimulation

HDL-C high-density lipoprotein-cholesterol

HOMA-IR homeostatic model assessment insulin resistance

HRR heart rate reserve

ISI-matsuda insulin sensitivity index

LDL-C low-density lipoprotein-cholesterol

RT resistance training

RCT randomised controlled trial

SBP systolic blood pressure

SCI spinal cord injury

TC total cholesterol

TG triglycerides

Persons with a spinal cord injury (SCI) are at an increased risk of cardiovascular disease and diabetes compared to able-bodied individuals [1, 2]. The risk of developing these chronic diseases is raised in individuals who present with a clustering of associated risk factors including: obesity, insulin resistance, dyslipidaemia, and hypertension, or as commonly referred to, cardiometabolic syndrome (CMS) [3]. The International Diabetes Federation defines CMS as central obesity (indicated by waist circumference), plus the presence (or treatment) of two of more of the following: hypertriglyceridemia (≥ 1.7 mmol/L), reduced high-density lipoprotein-cholesterol (HDL-C) (< 1.03 mmol/L for men, < 1.29 mmol/L for women), hypertension (systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg), and raised fasting plasma glucose (≥ 5.6 mmol/L, or diagnosed with type 2 diabetes) [4]. A waist circumference greater than 94 cm and/or a body mass index of greater than 22 kg/m^2 have been suggested as suitable cut-points to define central obesity in SCI [5, 6]. The prevalence of CMS in chronic SCI appears to be high; with the largest study to date ($n=473$) reporting a prevalence rate of 57.5% [7].

There is strong evidence that exercise is an effective countermeasure for the prevention of chronic disease and the treatment of CMS risk factors in the able-bodied population [8]. This has allowed national and global health organisations to produce guidelines regarding the total volume and intensity of physical activity (minimum of 150 min/week of moderate-intensity, or 75 minutes/week of vigorous-intensity) required to improve cardiometabolic health [9, 10]. However, as the most recent systematic review of the effect of exercise on health in SCI concluded, the evidence base for spinal cord injured persons “lags far behind” that for the general population [11]. This review formed the basis for the latest SCI-exercise guidelines, which recommend adults with a chronic SCI perform a minimum of 90 min/week of moderate-to-vigorous intensity aerobic exercise to improve cardiometabolic health [12]. Additional systematic reviews have also reported beneficial effects of exercise on specific CMS risk

factors, including systemic inflammation (C - reactive protein) and obesity (fat mass and waist circumference) in persons with chronic SCI [13, 14].

Since the last systematic search of the literature by van der Scheer and colleagues (search date: 1st Jan 2016), several randomised controlled trials assessing the effect of exercise training on CMS risk factors in SCI have been published. However, this systematic review did not address clinical thresholds for CMS risk factors at baseline, the magnitude of change following exercise training, and how different exercise modalities may impact specific individual CMS biomarkers. These questions are important for practitioners prescribing exercise to patients presenting with CMS risk factors, and researchers designing future studies in this field. A review which addresses these importance issues and focuses specifically on how different forms of exercise impacts on individual CMS risk factors in chronic SCI is therefore required. The aim of this systematic review is to determine the effect of different exercise modality interventions on CMS risk factors in adults with chronic SCI.

METHODS

The study inclusion criteria and planned analysis were specified in advance (PROSPERO:CRD42018105110) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed [15]. The databases of PubMed, Web of Science, EMBASE, and Scopus (Elsevier) were searched on 22nd August 2018, using a search strategy formulated based on a similar previous systematic review [11]. The search was repeated on 31st July 2019 to identify any additional articles prior to publication. The search strategy was piloted to ensure known articles were included and reviewed by two authors (MF & TN). The full search strategy for PubMed is presented in Supplement 1 as an exemplar. Briefly, the search was performed by combining key words associated with SCI (e.g., “paraplegia”, “spinal cord lesion”), exercise, (e.g., “physical activity”, “resistance training”,

“functional electrical stimulation”) and CMS risk factors (e.g., “glucose”, “BMI”, “blood pressure”). The reference list of included items and previous systematic reviews were checked and further articles identified. The final step involved hand-searching the journals which had returned the highest proportion of articles in the initial search, to identify any additional studies (e.g. Journal of Spinal Cord Medicine (1982-2018) and Archives of Physical Medicine and Rehabilitation (1985-2018)).

Titles and abstracts of retrieved articles were independently screened for relevance by two reviewers (MF & TN). The same two reviewers independently assessed the full text of relevant articles for eligibility. In the event of any disagreements in article selection, a third reviewer (JB) made the final decision. Articles were included if they met the criteria according to the PICOS structure: i) *participants* - $\geq 50\%$ of participants were aged ≥ 18 years old, and had a chronic SCI (≥ 1 year post-injury), ii) *intervention* - included an exercise training programme (any, or combination of: voluntary upper-body exercise, lower-body functional electrical stimulation (FES), and assisted ambulation training) lasting ≥ 2 weeks, iii) *comparison* – studies comparing exercise intervention to a control group or pre-intervention data, iv) *outcomes* - study included at least one CMS risk factor as an outcome variable (see Table 1) [4], and v) *study design* - study employed and reported quantitative statistical analysis to determine the impact of the exercise intervention on the relevant CMS risk outcome(s) (i.e. case reports and case-series were excluded), and was published in an English-language peer-reviewed journal (i.e. abstracts and conference proceedings were excluded) between 1st January 1970 and the final search date. Studies involving solely neuromuscular electrical stimulation (NMES) with no functional movement and passive cycling were excluded on the basis that the skeletal muscle contractions produced during these activities do not directly produce a functional movement, and therefore cannot be classed as exercise, *per se*. Studies assessing the impact of exercise on solely blood pressure amongst tetraplegics were excluded on the basis that the aim

of the exercise intervention was to increase resting blood pressure, and therefore was not reflective of a CMS risk factor (i.e. hypertension).

Two articles did not identify participants' time since injury [16, 17]. The corresponding authors were contacted by email and asked to provide clarification and given two weeks to respond. Both articles were excluded as the corresponding authors were unable to provide this information.

Two reviewers (MF and JM) independently evaluated the quality of included studies using a modified Downs and Black scale [18]. In the modified version, the scoring for question 27 (relating to statistical power) is simplified to "Yes" (1) or "No" (0). In the event of any discrepancies in scoring, discussion between the reviewers was used to reach a consensus. The total Downs & Black score for each article was expressed as a percentage of the maximum score possible (28) to allow categorisation of study quality [19]. Articles were classified as high ($\geq 66.7\%$), fair (between 50.0% and 66.6%), or low ($< 50.0\%$) quality [19].

An insufficient number of studies examined the same outcomes following similar exercise modalities, precluding a meta-analysis. Therefore, a coding system [19] was used to summarise the effect of different exercise training modalities on each CMS risk factor (Table 2). If 0-33% of studies reported a statistically significant change in a specific CMS risk factor following exercise training, the result was categorised as 'no effect'. If 34-59% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as 'inconsistent'. If 60-100% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as 'positive'. If four or more studies reported the same effect, the result was highlighted in bold to indicate a consistent finding. The findings from one particular study [20] were counted as non-significant for summary coding, due to the significance being set at $p < 0.10$, with actual p

values not reported. Data extraction was performed by MF, and later checked independently by TN, JM, and JB.

To aid interpretation of results, group average values at baseline for body mass index ($\geq 22 \text{ kg/m}^2$) [6], waist circumference ($> 94 \text{ cm}$) [5], triglycerides (TG) ($\geq 1.7 \text{ mmol/L}$), total cholesterol (TC) ($\geq 5 \text{ mmol/L}$), low-density lipoprotein (LDL-C) ($> 3 \text{ mmol/L}$), HDL-C ($< 1.03 \text{ mmol/L}$), fasting glucose ($\geq 5.6 \text{ mmol/L}$), systolic blood pressure (SBP) ($\geq 130 \text{ mmHg}$), and diastolic blood pressure (DBP) ($\geq 85 \text{ mmHg}$) [4] were highlighted to indicate that they can be classified as clinically high, according to the International Diabetes Federation and SCI-specific guidelines (Tables 3-9).

The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (e.g. oral glucose tolerance test) and categorized using indices such as ISI-matsuda.

RESULTS

The initial database search yielded a total of 2450 unique records, of which 2245 were excluded following title and abstract screening. An additional 10 articles were retrieved from; hand-searching of relevant journals ($n=1$), relevant systematic reviews ($n=2$), the associated reference list of an included paper ($n=4$), and the updated search ($n=3$). Therefore, the full-text of 215 studies were subsequently assessed, three papers [21-23] contained data presented in another article, and these were removed from all analysis, leaving 65 articles for final review. The study selection process is detailed in Figure 1.

There was substantial agreement between reviewers for title and abstract screening ($k=0.635$, 95% CI: 0.581, 0.689), and almost perfect agreement for the full-text screening ($k=0.880$, 95% CI: 0.811, 0.949) [24].

We identified studies as pre-post designs ($n=47$), RCTs ($n=15$), non-randomised controlled trials ($n=2$), and a retrospective cohort study ($n=1$). Numerous studies utilised arm-cranking ($n=9$), wheelchair ergometry ($n=3$), wheelchair treadmill propulsion ($n=2$), or hand-cycling ($n=2$). These 16 studies were grouped together for analysis as voluntary upper-body aerobic exercise (Table 3). Seven studies utilised upper-body resistance training (RT) (with or without upper-body aerobic exercise) (Table 4). The most common exercise modality was FES-cycling ($n=17$) (Table 5). Six studies utilised FES-resistance training (FES-RT) exercise (in the form of non-isometric knee extensions), and three studies involved a combination of FES-cycling and FES-RT (Table 6). Studies which involved hybrid functional electrical stimulation (FES)-cycling ($n=4$) or FES-rowing ($n=4$) were grouped together as they both involve lower-body FES combined with voluntary upper-body aerobic exercise (Table 7). Several studies utilised solely body weight supported treadmill training ($n=6$), FES-walking, exoskeletal body weight supported treadmill training ($n=1$), or robotic body weight supported treadmill training ($n=1$). These 10 studies were grouped together for analysis (Table 8). Studies that involved a combination of upper-body aerobic, upper-body RT and neuromuscular stimulation ($n=1$), or a combination of lower-body FES-RT, and BWSTT ($n=1$), were not grouped for qualitative analysis (Table 9).

Intervention durations ranged from four to 52 weeks, with the most common length of 12 weeks ($n=14$). Training frequency ranged from 1 to 7 sessions per week, with three times per week the most common frequency of exercise performed ($n=35$). No serious adverse events were reported in any of the included studies.

198 Sample sizes ranged from four to 48. Only seven studies reported a-priori sample size
199 calculations, and four of these met their target sample size (Table 10). There was a total of 872
200 participants (658 men, 110 women, 104 NR) (Table 10). There were nine studies classified as
201 high quality, 35 studies classified as fair quality, and 21 studies classified as low quality. The
202 most commonly assessed outcome measures for obesity, glycaemic control, dyslipidaemia,
203 inflammation, vascular dysregulation, and thrombotic state were body mass (n=28),
204 interleukin-6 (n=7), HDL-C (n=23), fasting glucose (n=18), PAI-1 (n=3), and systolic blood
205 pressure (n=22), respectively. No studies reported outcome measures of hip circumference,
206 liver fat content, apolipoprotein B, or proinsulin.

DISCUSSION

There are consistent findings that voluntary upper-body aerobic exercise ($>75\%$ HR_{MAX}) is effective in reducing waist circumference, and improving hepatic insulin sensitivity (i.e. fasting insulin concentration and HOMA-IR), however it does not appear to improve fasting glucose concentrations, lipid profile or resting blood pressure in persons with chronic SCI. The addition of upper-body RT appears to have an inconsistent effect on lipid profiles, but given the limited number of high-quality studies on combined exercise modalities, more research is needed in this area. FES-cycling may improve outcomes relating to peripheral insulin sensitivity (i.e. ability of the skeletal muscle to dispose of glucose), but more high-quality studies are required to strengthen the available evidence. There is insufficient evidence to conclude if FES-resistance training, FES-hybrid, FES-rowing, or assisted ambulation training improves any of these CMS risk factors.

Four [27, 25, 34, 33] of the six studies utilising upper-body aerobic exercise reported a reduction in supine waist circumference (-1.9 to -3.7 cm, ES: 0.26-2.67), indicating that this form of exercise is effective for reducing central obesity. A reduction in waist circumference (-2.5 cm) was achieved with as few as 64 min/week of exercise at 65-75% HRR [25], though this reduction did not translate to any change in android fat mass [25]. There was also no change in visceral adipose tissue [26] following 180 min/week at 60-65% $\dot{V}O_{2peak}$ of upper-body aerobic exercise. Future studies should combine both surrogate and gold-standard measures (i.e. DEXA/CT derived) of central obesity/adiposity to further elucidate changes in body composition. Given the relatively small skeletal muscle mass involved in upper-body aerobic exercise, it is perhaps unsurprising that there were consistent findings that body mass and BMI were unchanged, as reported in a previous systematic review [14]. Whilst not part of the search strategy, only one study in this category measured free-living energy intake and expenditure

during the exercise intervention [26]. In order to better understand the isolated impact of prescribed exercise interventions on energy balance and body composition, future studies should also attempt to estimate total energy intake and total energy expenditure. This would account for any compensatory changes in diet or exercise behaviours, providing a better understanding of the overall impact of exercise interventions on energy balance in SCI [90]. Guidelines for measuring these variables in persons with chronic SCI have been published elsewhere [91].

Four [25, 28, 26, 33] of the five studies that measured fasting insulin resistance by HOMA-IR and/or fasting insulin concentrations reported a reduction (22-40%, ES: 1.07-1.78) following upper-body aerobic exercise, suggesting that this form of exercise is effective at improving hepatic insulin sensitivity (i.e. ability of the liver to dispose of glucose). The single study [31] to find no statistically significant change in fasting insulin concentration following upper-body aerobic exercise, reported that all five participants had a lower insulin concentration (22-76%, ES: 0.41) post-training, indicating that the study simply lacked the statistical power to demonstrate an effect. Despite the improvement in hepatic insulin sensitivity [92] observed following upper-body aerobic exercise, the three studies [26, 28, 31] that measured outcomes relating to peripheral insulin sensitivity [93] found no changes following training. This is likely as a result of the limited skeletal muscle mass involved (i.e. limited sink for glucose disposal). Furthermore, the upper-body skeletal musculature is usually already well-conditioned from habitual wheelchair propulsion, meaning that moderate-intensity upper-body exercise is likely an insufficient stimulus to substantially promote molecular adaptations (e.g. GLUT4 translocation, mitochondrial biogenesis) associated with improved peripheral insulin sensitivity [94]. A high quality study reported no improvement in glucose or insulin area under the curve despite 180 min/week of exercise at 60-65% $\dot{V}O_{2peak}$ [26]. This suggests that even large volumes of upper-body aerobic exercise above the

recommended guidelines of 90 min/week [12] may be insufficient to improve markers of peripheral insulin sensitivity.

There are also numerous studies indicating that upper-body aerobic exercise alone does not improve fasting glucose, resting blood pressure (SBP, DBP), or lipid profiles (TC, HDL-C, LDL-C, and TG). All eight studies [25, 26, 28, 31-35] measuring fasting glucose reported no change following upper-body aerobic exercise. However, only one study [34] reported a clinically elevated group mean glucose concentration at baseline (≥ 5.6 mmol/L). Nine studies [29, 35, 38, 39, 25, 26, 34, 32, 31] measured changes in resting blood pressure following upper-body aerobic exercise. The only study [34] where participants presented with clinically elevated systolic blood pressure (≥ 130 mmHg) at baseline reported a reduction (3 mmHg, ES: 0.66) following 10 weeks of exercise training (4 sessions/week 50-70% HRR, 60 min). Thus, a basement effect may explain the lack of significant changes in fasting glucose and resting blood pressure in participants presenting with healthy values at baseline. Eight studies measured TG, TC, HDL-C, or LDL-C [25, 26, 28, 32-35, 20] following upper-body aerobic exercise, including four with clinically high mean concentrations at baseline. Only two studies reported a significant reduction in any variable. One study [34] reported a 25% reduction (ES: 0.31) in TG in participants with a clinically elevated mean concentrations at baseline (≥ 1.7 mmol/L). One study reported improvements in HDL-C, LDL-C, TC: HDL-C and TG following 60 mins/week at 70-80% HRR, however the threshold for significance was set at $p < 0.10$ [40]. It therefore appears that upper-body aerobic exercise may not be an adequate stimulus to improve blood lipid profile irrespective of baseline values. This is likely due to the low energy expenditure achieved through upper-body exercise, which appears to drive changes in the lipid profile [95].

Upper-body RT (with or without aerobic exercise) appears to reduce central obesity, with three [42-44] out of four studies reporting a reduction in waist circumference (-

1.0 to -2.6 cm) or waist to hip ratio (-0.02). These changes were accompanied by a decrease in whole-body fat mass and visceral adipose tissue following 120 min/week of training (3 x 10 of 50-70% 1RM, 20 min at 3-6 RPE) [42]. Upper-body RT (with or without aerobic exercise) may elicit improvements in lipid profile, with four [43-45, 40] out of the five retrieved studies reporting a beneficial effect of at least one marker (TC, HDL-C, LDL-C, TC: HDL-C, and TG). However, more studies are needed to determine this, particularly given the high-quality study reporting no change in the lipid profile following 16-weeks of twice-weekly combined training [42].

Five [50, 54, 58, 60, 62] of the six studies to measure outcomes relating to peripheral insulin sensitivity reported a significant improvement following FES-cycling. The largest of these studies (n=18) [54] reported a significant reduction in glucose and insulin at multiple time-points during a 2-h oral glucose tolerance test following 10 weeks of exercise (2-3 sessions/week, 30 min). However, four of these studies were rated as low quality, and therefore more high-quality studies are needed to confirm if FES-cycling can improve peripheral insulin sensitivity, which upper-body exercise appears unable to achieve. Surprisingly, we identified no RCT's assessing the efficacy of FES-cycling compared to a true control group (i.e. passive cycling or stretching), which should be addressed in future research. Four studies reported no change in body mass following FES-hybrid or FES-rowing training. There was a distinct lack of training studies with sufficient breadth of outcomes to make any other meaningful conclusions on the effect of FES-RT, FES-hybrid, FES-rowing and assisted ambulation on CMS risk factors. Nonetheless, given that hybrid training (2 sessions/week, 18-32 min, 65-75% HRR) [25] improved a multitude of CMS risk factors (waist circumference, android fat percentage, TG, DBP), and that different exercise modalities appear to offer specific benefits to CMS risk factors, other rigorously conducted prospective studies assessing multimodal (e.g.

FES-cycling combined with upper-body aerobic and resistance exercise) interventions should be conducted in this area of promise.

This review has highlighted the lack of research assessing novel markers of CMS risk, including outcomes relating to inflammation, DEXA/CT derived measures of central adiposity, and endothelial function. It is clear that many studies in the area recruit a convenience sample of relatively active and lean individuals, who are not reflective of the wider, chronic SCI population (i.e. poor metabolic health), which should be considered when interpreting results. For example, individuals with SCI have a significantly lower HDL-C compared to able-bodied controls (1.06 vs 1.28 mmol/L) [96], however only five of the 23 studies to measure HDL-C had a clinically low mean concentration at baseline (<1.03 mmol/L). As is widely acknowledged, this review has also confirmed the existing evidence base of exercise and CMS risk in SCI lacks sufficiently powered (four in total identified), high-quality studies (eight in total identified). However, this review identified 16 additional studies, published since the previous systematic review by van der Scheer and colleagues [11] that were all categorised as fair or high quality, including eight RCT's.

Study Limitations

The main limitation of this systematic review is the use of summary coding to draw conclusions regarding the effect of each exercise modality on specific CMS risk factors. Due to the variability in CMS risk factors measured, exercise modes and training parameters (i.e. exercise intensity and volume), and participant characteristics (i.e. paraplegic vs. tetraplegic), a meta-analysis was not possible. Whilst the coding system provides a useful assessment of the consistency of findings in the field, it uses arbitrary classifications and does not distinguish studies of differing quality. However, when studies rated as 'low-quality' were removed from this analysis (Supplement 3), the conclusions remained unchanged, with the exception of

331 potential of FES-cycling to improve peripheral insulin sensitivity. Further, given that the vast
332 majority of included studies lacked sufficient statistical power, there is a risk of a type II error
333 in the conclusions formed. Finally, this review did not include acute SCI as van der Scheer and
334 colleagues [11] determined there was an “absence of high-quality, consistent evidence” in this
335 area, a view which still appears to be true.

CONCLUSIONS

In summary, this systematic review has provided evidence that in adults with chronic SCI, upper-body aerobic exercise improves outcomes relating to central obesity and hepatic insulin sensitivity, but is not sufficient to improve fasting glucose, lipid profiles, or resting blood pressure. Practitioners should consider prescribing moderate-to-vigorous intensity (>75% HR_{MAX}) upper-body aerobic exercise to improve fasting glycaemic control and central obesity. To elicit improvements in lipid profile, this should be combined with upper-body resistance training. More high-quality randomised controlled trials assessing novel markers of CMS and responses to combined exercise interventions (e.g. aerobic exercise with resistance training), high-intensity exercise interventions, and FES-based exercise are needed to inform and refine evidence-based exercise guidelines for the prevention and management of CMS in this population.

REFERENCES

1. Cragg JJ, Noonan VK, Dvorak M, Krassioukov A, Mancini GB, Borisoff JF. Spinal cord injury and type 2 diabetes: results from a population health survey. *Neurology*. 2013;81(21):1864-8. doi:10.1212/01.wnl.0000436074.98534.6e.
2. Cragg JJ, Noonan VK, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury: results from a national population health survey. *Neurology*. 2013;81(8):723-8. doi:10.1212/WNL.0b013e3182a1aa68.
3. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med*. 2005;165(22):2644-50. doi:10.1001/archinte.165.22.2644.
4. Alberti K, Zimmet P, Shaw J. Metabolic syndrome - a new world-wide definition. A consensus statement from the international diabetes federation. *Diabetic Medicine*. 2006;23(5):469-80. doi:10.1111/j.1464-5491.2006.01858.x.
5. Ravensbergen HJC, Lear SA, Claydon VE. Waist Circumference Is the Best Index for Obesity-Related Cardiovascular Disease Risk in Individuals with Spinal Cord Injury. *Journal of Neurotrauma*. 2014;31(3):292-300. doi:10.1089/neu.2013.3042.
6. Laughton GE. Lowering body mass index cutoffs better identifies obese persons with spinal cord injury. *Spinal Cord*. 2009;47(10):757-63.
7. Gater DR, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med*. 2019; 42:86-93. doi:10.1080/10790268.2017.1423266.
8. Booth FW, Roberts CK, Laye MJ. Lack of Exercise Is a Major Cause of Chronic Diseases. *Compr Physiol*. 2012;2(2):1143-211. doi:10.1002/cphy.c110025.

- 372 9. Piercy K, Troiano R, Ballard RM, Carlson SA, Fulton J, Galuska D et al. The Physical
373 Activity Guidelines for Americans. *J Am Med Assoc.* 2018;320(19):2020-8.
374 doi:10.1001/jama.2018.14854.
- 375 10. WHO. Global recommendations on physical activity for health. 2010.
- 376 11. van der Scheer JW, Ginis KAM, Ditor DS, Goosey-Tolfrey VL, Hicks AL, West CR et
377 al. Effects of exercise on fitness and health of adults with spinal cord injury A systematic
378 review. *Neurology.* 2017;89(7):736-45. doi:10.1212/wnl.0000000000004224.
- 379 12. Ginis KAM, van der Scheer JW, Latimer-Cheung AE, Barrow A, Bourne C, Carruthers P
380 et al. Evidence-based scientific exercise guidelines for adults with spinal cord injury: an
381 update and a new guideline. *Spinal Cord.* 2018;56(4):308-21. doi:10.1038/s41393-017-0017-
382 3.
- 383 13. Neefkes-Zonneveld CR, Bakkum AJ, Bishop NC, van Tulder MW, Janssen TW. Effect of
384 Long-Term Physical Activity and Acute Exercise on Markers of Systemic Inflammation in
385 Persons With Chronic Spinal Cord Injury: A Systematic Review. *Arch Phys Med Rehabil.*
386 2015;96(1):30-42. doi:10.1016/j.apmr.2014.07.006.
- 387 14. Shojaei MH, Alavinia SM, Craven BC. Management of obesity after spinal cord injury: a
388 systematic review. *J Spinal Cord Med* 2017;40(6):783-94.
389 doi:10.1080/10790268.2017.1370207.
- 390 15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA et al. The
391 PRISMA statement for reporting systematic reviews and meta-analyses of studies that
392 evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339.
393 doi:10.1136/bmj.b2700.
- 394 16. El-Sayed MS, Younesian A. Lipid profiles are influenced by arm cranking exercise and
395 training in individuals with spinal cord injury. *Spinal Cord.* 2005;43(5):299-305.
396 doi:10.1038/sj.sc.3101698.

- 397 17. Petrofsky JS, Stacy R. The effect of training on endurance and the cardiovascular
398 responses of individuals with paraplegia during dynamic exercise induced by functional
399 electrical stimulation. *Eur J Appl Physiol Occup Physiol*. 1992;64(6):487-92.
- 400 18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the
401 methodological quality both of randomised and non-randomised studies of health care
402 interventions. *J Epidemiol Community Health*. 1998;52(6):377-84.
403 doi:10.1136/jech.52.6.377.
- 404 19. Batacan RB, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high- intensity
405 interval training on cardiometabolic health: a systematic review and meta-analysis of
406 intervention studies. *Br J Sports Med*. 2017; 51: 494-503. doi:10.1136/bjsports-2015-095841.
- 407 20. Hooker SP, Wells CL. Effects of low- and moderate-intensity training in spinal cord-
408 injured persons. *Med Sci Sports Exerc*. 1989;21(1):18-22.
- 409 21. Ordonez FJ, Rosety MA, Camacho A, Rosety I, Diaz AJ, Fornieles G et al. Arm-cranking
410 exercise reduced oxidative damage in adults with chronic spinal cord injury. *Arch Phys Med*
411 *Rehabil*. 2013;94(12):2336-41. doi:10.1016/j.apmr.2013.05.029.
- 412 22. Rosety-Rodriguez M, Rosety I, Fornieles G, Rosety JM, Elosegui S, Rosety MA et al. A
413 short-term arm-crank exercise program improved testosterone deficiency in adults with
414 chronic spinal cord injury. *International Braz J Urol*. 2014;40(3):367-72. doi:10.1590/s1677-
415 5538.ibju.2014.03.10.
- 416 23. Willoughby DS, Priest JW, Nelson M. Expression of the stress proteins, ubiquitin, heat
417 shock protein 72, and myofibrillar protein content after 12 weeks of leg cycling in persons
418 with spinal cord injury. *Arch Phys Med Rehabil*. 2002;83(5):649-54.
419 doi:10.1053/apmr.2002.31184.
- 420 24. Sim J. The Kappa Statistic in Reliability Studies: Use, Interpretation, and Sample Size
421 Requirements. *Physical Therapy*. 2005;85(3):257-69.

- 422 25. Bakkum AJ, Paulson TA, Bishop NC, Goosey-Tolfrey VL, Stolwijk-Swuste JM, van
423 Kuppevelt DJ et al. Effects of hybrid cycle and handcycle exercise on cardiovascular disease
424 risk factors in people with spinal cord injury: A randomized controlled trial. *J Rehabil Med*.
425 2015;47(6):523-30. doi:10.2340/16501977-1946.
- 426 26. Nightingale TE, Walhin JP, Thompson D, Bilzon LJ. Impact of Exercise on
427 Cardiometabolic Component Risks in Spinal Cord-injured Humans. *Med Sci Sports Exerc*.
428 2017;49(12):2469-77. doi:10.1249/mss.0000000000001390.
- 429 27. Rosety-Rodriguez M, Camacho A, Rosety I, Fornieles G, Rosety MA, Diaz AJ et al.
430 Low-Grade Systemic Inflammation and Leptin Levels Were Improved by Arm Cranking
431 Exercise in Adults With Chronic Spinal Cord Injury. *Arch Phys Med Rehabil*.
432 2014;95(2):297-302. doi:10.1016/j.apmr.2013.08.246.
- 433 28. Bresnahan JJ, Farkas GJ, Clasey JL, Yates JW, Gater DR. Arm crank ergometry improves
434 cardiovascular disease risk factors and community mobility independent of body composition
435 in high motor complete spinal cord injury. *J Spinal Cord Med*. 2018; 42(3): 272-80.
436 doi:10.1080/10790268.2017.1412562.
- 437 29. Han DS, Hsiao MY, Wang TG, Chen SY, Yang WS. Association of serum myokines and
438 aerobic exercise training in patients with spinal cord injury: An observational study. *BMC*
439 *Neurology*. 2016;16(1). doi:10.1186/s12883-016-0661-9.
- 440 30. McLean KP, Skinner JS. Effect of body training position on outcomes of an aerobic
441 training study on individuals with quadriplegia. *Arch Phys Med Rehabil*. 1995;76(2):139-50.
442 doi:10.1016/S0003-9993(95)80023-9.
- 443 31. Gorgey AS, Graham ZA, Bauman WA, Cardozo C, Gater DR. Abundance in proteins
444 expressed after functional electrical stimulation cycling or arm cycling ergometry training in
445 persons with chronic spinal cord injury. *J Spinal Cord Med*. 2017;40(4):439-48.
446 doi:10.1080/10790268.2016.1229397.

- 447 32. Akkurt H, Karapolat HU, Kirazli Y, Kose T. The effects of upper extremity aerobic
448 exercise in patients with spinal cord injury: A randomized controlled study. *Eur J Phys*
449 *Rehabil Med.* 2017;53(2):219-27. doi:10.23736/s1973-9087.16.03804-1.
- 450 33. Kim DI, Lee H, Lee BS, Kim J, Jeon JY. Effects of a 6-Week Indoor Hand-Bike Exercise
451 Program on Health and Fitness Levels in People With Spinal Cord Injury: A Randomized
452 Controlled Trial Study. *Arch Phys Med Rehabil.* 2015;96(11):2033-U325.
453 doi:10.1016/j.apmr.2015.07.010.
- 454 34. Horiuchi M, Okita K. Arm-Cranking Exercise Training Reduces Plasminogen Activator
455 Inhibitor 1 in People With Spinal Cord Injury. *Arch Phys Med Rehabil.* 2017;98(11):2174-
456 80. doi:10.1016/j.apmr.2017.02.007.
- 457 35. Midha M, Schmitt JK, Sclater M. Exercise effect with the wheelchair aerobic fitness
458 trainer on conditioning and metabolic function in disabled persons: A pilot study. *Arch Phys*
459 *Med Rehabil.* 1999;80(3):258-61. doi:10.1016/s0003-9993(99)90135-1.
- 460 36. Mukherjee G, Bhowmik P, Samanta A. Physical fitness training for wheelchair
461 ambulation by the arm crank propulsion technique. *Clin Rehabil.* 2001;15(2):125-32.
462 doi:10.1191/026921501666069173.
- 463 37. Gass GC, Watson J, Camp EM, Court HJ, McPherson LM, Redhead P. The effects of
464 physical training on high level spinal lesion patients. *Scand J Rehabil Med.* 1980;12(2):61.
- 465 38. Yim SY, Cho KJ, Park CI, Yoon TS, Han DY, Kim SK et al. Effect of wheelchair
466 ergometer training on spinal cord-injured paraplegics. *Yonsei Med. J.* 1993;34(3):278-86.
467 doi:10.3349/ymj.1993.34.3.278.
- 468 39. Davis GM, Shephard RJ, Leenen FH. Cardiac effects of short term arm crank training in
469 paraplegics: echocardiographic evidence. *Eur J Appl Physiol Occup Physiol.* 1987;56(1):90-
470 6.

- 471 40. Hooker SP, Wells CL. Effects of low- and moderate-intensity training in spinal cord-
 472 injured persons. *Med Sci Sports Exerc.* 1989;21(1):18-22. doi:10.1249/00005768-
 473 198902000-00004.
- 474 41. Giangregorio L, Craven C, Richards K, Kapadia N, Hitzig SL, Masani K et al. A
 475 randomized trial of functional electrical stimulation for walking in incomplete spinal cord
 476 injury: Effects on body composition. *J Spinal Cord Med.* 2012;35(5):351-60.
 477 doi:10.1179/2045772312y.0000000041.
- 478 42. de Zepetnek JOT, Pelletier CA, Hicks AL, MacDonald MJ. Following the Physical
 479 Activity Guidelines for Adults With Spinal Cord Injury for 16 Weeks Does Not Improve
 480 Vascular Health: A Randomized Controlled Trial. *Arch Phys Med Rehabil.* 2015;96(9):1566-
 481 75. doi:10.1016/j.apmr.2015.05.019.
- 482 43. Mogharnasi M, TaheriChadorneshin H, Papoli-Baravati SA, Teymuri A. Effects of upper-
 483 body resistance exercise training on serum nesfatin-1 level, insulin resistance, and body
 484 composition in obese paraplegic men. *Disabil Health J.* 2019; 12(1): 29-34.
 485 doi:10.1016/j.dhjo.2018.07.003.
- 486 44. Kim D-I, Taylor JA, Tan CO, Park H, Kim JY, Park S-Y et al. A pilot randomized
 487 controlled trial of 6-week combined exercise program on fasting insulin and fitness levels in
 488 individuals with spinal cord injury. *Eur Spine J.* 2019; 28(5); 1082-1091.
 489 doi:10.1007/s00586-019-05885-7.
- 490 45. Cugusi L, Solla P, Serpe R, Pilia K, Pintus V, Madeddu C et al. Effects of an adapted
 491 physical training on functional status, body composition and quality of life in persons with
 492 spinal cord injury paraplegia: a pilot study. *Med Sport (Roma).* 2015;68(3):473-85.
- 493 46. Hicks AL, Adams MM, Martin Ginis K, Giangregorio L, Latimer A, Phillips SM et al.
 494 Long-term body-weight-supported treadmill training and subsequent follow-up in persons

- 495 with chronic SCI: effects on functional walking ability and measures of subjective well-
 496 being. *Spinal Cord*. 2005;43(5):291-8. doi:10.1038/sj.sc.3101710.
- 497 47. Nash MS, Jacobs PL, Mendez AJ, Goldberg RB. Circuit resistance training improves the
 498 atherogenic lipid profiles of persons with chronic paraplegia. *J Spinal Cord Med*.
 499 2001;24(1):2-9.
- 500 48. Allison DJ, Chapman B, Wolfe D, Sequeira K, Hayes K, Ditor DS. Effects of a functional
 501 electrical stimulation-assisted cycling program on immune and cardiovascular health in
 502 persons with spinal cord injury. *Top Spinal Cord Inj Rehabil*. 2016;22(1):71-8.
 503 doi:10.1310/sci2201-71.
- 504 49. Sadowsky CL, Hammond ER, Strohl AB, Commean PK, Eby SA, Damiano DL et al.
 505 Lower extremity functional electrical stimulation cycling promotes physical and functional
 506 recovery in chronic spinal cord injury. *J Spinal Cord Med*. 2013;36(6):623-31.
 507 doi:10.1179/2045772313Y.00000000101.
- 508 50. Jeon JY, Weiss CB, Steadward RD, Ryan E, Burnham RS, Bell G et al. Improved glucose
 509 tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with
 510 spinal cord injury. *Spinal Cord*. 2002;40(3):110-7. doi:10.1038/sj/sc/3101260.
- 511 51. Gerrits HL. Peripheral vascular changes after electrically stimulated cycle training in
 512 people with spinal cord injury. *Arch Phys Med Rehabil*. 2001;82(6):832-40.
- 513 52. Liu CW, Chen SC, Chen CH, Chen TW, Chen JJ, Lin CS et al. Effects of functional
 514 electrical stimulation on peak torque and body composition in patients with incomplete spinal
 515 cord injury. *Kaohsiung J Med Sci*. 2007;23(5):232-40.
- 516 53. Faghri PD, Glaser RM, Figoni SF. Functional electrical stimulation leg cycle ergometer
 517 exercise: training effects on cardiorespiratory responses of spinal cord injured subjects at rest
 518 and during submaximal exercise. *Arch Phys Med Rehabil*. 1992;73(11):1085-93.

- 519 54. Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z et al. Functional electrical
520 stimulation cycling improves body composition, metabolic and neural factors in persons with
521 spinal cord injury. *J Electromyogr Kinesiol.* 2009;19(4):614-22.
522 doi:10.1016/j.jelekin.2008.03.002.
- 523 55. Robergs RA, Appenzeller O, Qualls C, Aisenbrey J, Krauss J, Kopriva L et al. Increased
524 endothelin and creatine kinase after electrical stimulation of paraplegic muscle. *J Appl*
525 *Physiol.* 1993;75(6):2400-5. doi:10.1152/jappl.1993.75.6.2400.
- 526 56. Hjeltne N, Aksnes AK, Birkeland KI, Johansen J, Lannem A, WallbergHenriksson H.
527 Improved body composition after 8 wk of electrically stimulated leg cycling in tetraplegic
528 patients. *Am J Physiol Regul Integr Comp Physiol.* 1997;273(3):R1072-R9.
- 529 57. Kahn NN, Feldman SP, Bauman WA. Lower-Extremity Functional Electrical Stimulation
530 Decreases Platelet Aggregation and Blood Coagulation in Persons With Chronic Spinal Cord
531 Injury: A Pilot Study. *J Spinal Cord Med.* 2010;33(2):150-8.
532 doi:10.1080/10790268.2010.11689690.
- 533 58. Hjeltne N, Galuska D, Bjornholm M, Aksnes AK, Lannem A, Zierath JR et al. Exercise-
534 induced overexpression of key regulatory proteins involved in glucose uptake and
535 metabolism in tetraplegic persons: molecular mechanism for improved glucose homeostasis.
536 *FASEB J.* 1998;12(15):1701-12.
- 537 59. Lammers G, Van Duijnhoven NTL, Hoenderop JG, Horstman AM, De Haan A, Janssen
538 TWJ et al. The identification of genetic pathways involved in vascular adaptations after
539 physical deconditioning versus exercise training in humans. *Exp Physiol.* 2013;98(3):710-21.
540 doi:10.1113/expphysiol.2012.068726.
- 541 60. Mohr T, Dela F, Handberg A, Biering-Sorensen F, Galbo H, Kjaer M. Insulin action and
542 long-term electrically induced training in individuals with spinal cord injuries. *Med Sci*
543 *Sports Exerc.* 2001;33(8):1247-52. doi:10.1097/00005768-200108000-00001.

- 544 61. Sköld C, Lönn L, Harms-Ringdahl K, Hultling C, Levi R, Nash M et al. Effects of
545 functional electrical stimulation training for six months on body composition and spasticity in
546 motor complete tetraplegic spinal cord-injured individuals. *J Rehabil Med.* 2002;34(1):25-32.
547 doi:10.1080/165019702317242677.
- 548 62. Chilibeck PD, Bell G, Jeon J, Weiss CB, Murdoch G, MacLean I et al. Functional
549 electrical stimulation exercise increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle.
550 *Metabolism.* 1999;48(11):1409-13. doi:10.1016/s0026-0495(99)90151-8.
- 551 63. Gorgey AS, Khalil R, Gill RS, Gater DR, Lavis TR, Cardozo C et al. Low-Dose
552 Testosterone and Evoked Resistance Exercise after Spinal Cord Injury TEREX-SCI on
553 Cardio-metabolic Risk Factors: An open-label randomized clinical trial. *J of Neurotrauma.*
554 2019. doi:10.1089/neu.2018.6136.
- 555 64. Gorgey AS, Mather KJ, Cupp HR, Gater DR. Effects of Resistance Training on Adiposity
556 and Metabolism after Spinal Cord Injury. *Med Sci Sports Exerc.* 2012;44(1):165-74.
557 doi:10.1249/MSS.0b013e31822672aa.
- 558 65. Rodgers MM, Glaser RM, Figoni SF, Hooker SP, Ezenwa BN, Collins SR et al.
559 Musculoskeletal responses of spinal cord injured individuals to functional neuromuscular
560 stimulation-induced knee extension exercise training. *J Rehabil Res Dev.* 1991;28(4):19-26.
- 561 66. Ryan TE, Brizendine JT, Backus D, McCully KK. Electrically Induced Resistance
562 Training in Individuals With Motor Complete Spinal Cord Injury. *Arch Phys Med Rehabil.*
563 2013;94(11):2166-73. doi:10.1016/j.apmr.2013.06.016.
- 564 67. Stoner L, Sabatier MJ, Mahoney ET, Dudley GA, McCully KK. Electrical stimulation-
565 evoked resistance exercise therapy improves arterial health after chronic spinal cord injury.
566 *Spinal Cord.* 2007;45(1):49-56. doi:10.1038/sj.sc.3101940.

- 567 68. Ragnarsson KT, Pollack S, O'Daniel Jr W, Edgar R, Petrofsky J, Nash MS. Clinical
568 evaluation of computerized functional electrical stimulation after spinal cord injury: A
569 multicenter pilot study. *Arch Phys Med Rehabil.* 1988;69(9):672-7.
- 570 69. Pollack SF, Axen K, Spielholz N, Levin N, Haas F, Ragnarsson KT. Aerobic training
571 effects of electrically induced lower extremity exercises in spinal cord injured people. *Arch*
572 *Phys Med Rehabil.* 1989;70(3):214-9.
- 573 70. Mahoney ET, Bickel CS, Elder C, Black C, Slade JM, Apple D et al. Changes in skeletal
574 muscle size and glucose tolerance with electrically stimulated resistance training in subjects
575 with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2005;86(7):1502-4.
576 doi:10.1016/j.apmr.2004.12.021.
- 577 71. Pacy PJ, Hesp R, Halliday DA, Katz D, Cameron G, Reeve J. Muscle and bone in
578 paraplegic patients, and the effect of functional electrical stimulation. *Clin Sci (Lond).*
579 1988;75(5):481-7.
- 580 72. Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training
581 and detraining in persons with spinal cord injury. *Arch Phys Med Rehabil.* 2006;87(4):474-
582 81. doi:10.1016/j.apmr.2005.11.005.
- 583 73. Kim DI, Park DS, Lee BS, Jeon JY. A six-week motor-driven functional electronic
584 stimulation rowing program improves muscle strength and body composition in people with
585 spinal cord injury: a pilot study. *Spinal Cord.* 2014;52(8):621-4. doi:10.1038/sc.2014.76.
- 586 74. Qiu S, Alzhab S, Picard G, Taylor JA. Ventilation Limits Aerobic Capacity after
587 Functional Electrical Stimulation Row Training in High Spinal Cord Injury. *Med Sci Sports*
588 *Exerc.* 2016;48(6):1111-9.
- 589 75. Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular
590 adaptations after hybrid training in spinal cord-injured subjects. *Med Sci Sports Exerc.*
591 2005;37(7):1112-8.

- 592 76. Wilbanks SR, Rogers R, Pool S, Bickel CS. Effects of functional electrical stimulation
593 assisted rowing on aerobic fitness and shoulder pain in manual wheelchair users with spinal
594 cord injury. *J Spinal Cord Med*. 2016;39(6):645-54. doi:10.1179/2045772315Y.00000000052.
- 595 77. Jeon JY, Hettinga D, Steadward RD, Wheeler GD, Bell G, Harber V. Reduced Plasma
596 Glucose and Leptin After 12 Weeks of Functional Electrical Stimulation-Rowing Exercise
597 Training in Spinal Cord Injury Patients. *Arch Phys Med Rehabil*. 2010;91(12):1957-9.
598 doi:10.1016/j.apmr.2010.08.024.
- 599 78. Hasnan N, Engkasan JP, Husain R, Davis GM. High-intensity virtual-reality arm plus
600 FES-leg interval training in individuals with spinal cord injury. *Biomed Tech (Berl)*.
601 2013;58(SUPPL. 1 TRACK-A). doi:10.1515/bmt-2013-4028
- 602 79. Gorman PH, Scott W, York H, Theyagaraj M, Price-Miller N, McQuaid J et al.
603 Robotically assisted treadmill exercise training for improving peak fitness in chronic motor
604 incomplete spinal cord injury: A randomized controlled trial. *J Spinal Cord Med*.
605 2016;39(1):32-44. doi:10.1179/2045772314y.00000000281.
- 606 80. Ditor DS, MacDonald MJ, Kamath MV, Bugaresti J, Adams M, McCartney N et al. The
607 effects of body-weight supported treadmill training on cardiovascular regulation in
608 individuals with motor-complete SCI. *Spinal Cord*. 2005;43(11):664-73.
609 doi:10.1038/sj.sc.3101785.
- 610 81. Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N, Hicks AL. Effects of
611 body weight-supported treadmill training on heart rate variability and blood pressure
612 variability in individuals with spinal cord injury. *J Appl Physiol*. 2005;98(4):1519-25.
613 doi:10.1152/jappphysiol.01004.2004.
- 614 82. Turiel M, Sitia S, Cicala S, Magagnin V, Bo I, Porta A et al. Robotic treadmill training
615 improves cardiovascular function in spinal cord injury patients. *Int J Cardiol*.
616 2011;149(3):323-9. doi:10.1016/j.ijcard.2010.02.010.

- 617 83. Giangregorio LM, Webber CE, Phillips SM, Hicks AL, Craven BC, Bugaresti JM et al.
618 Can body weight supported treadmill training increase bone mass and reverse muscle atrophy
619 in individuals with chronic incomplete spinal cord injury? *Appl Physiol Nutr Metab*.
620 2006;31(3):283-91. doi:10.1139/h05-036.
- 621 84. Karelis AD, Carvalho LP, Castillo MJ, Gagnon DH, Aubertin-Leheudre M. Effect on
622 body composition and bone mineral density of walking with a robotic exoskeleton in adults
623 with chronic spinal cord injury. *J Rehabil Med*. 2017;49(1):84-7. doi:10.2340/16501977-
624 2173.
- 625 85. Stewart BG, Tarnopolsky MA, Hicks AL, McCartney N, Mahoney DJ, Staron R et al.
626 Treadmill training-induced adaptations in muscle phenotype in persons with incomplete
627 spinal cord injury. *Muscle & Nerve*. 2004;30(1):61-8. doi:10.1002/mus.20046.
- 628 86. Phillips SM, Stewart BG, Mahoney DJ, Hicks AL, McCartney N, Tang JE et al. Body-
629 weight-support treadmill training improves blood glucose regulation in persons with
630 incomplete spinal cord injury. *J Appl Physiol*. 2004;97(2):716-24.
631 doi:10.1152/jappphysiol.00167.2004.
- 632 87. Klose KJ, Jacobs PL, Broton JG, Guest RS, NeedhamShropshire BM, Lebowhl N et al.
633 Evaluation of a training program for persons with SCI paraplegia using the Parastep(R)1
634 ambulation system .1. Ambulation performance and anthropometric measures. *Arch Phys*
635 *Med Rehabil*. 1997;78(8):789-93. doi:10.1016/s0003-9993(97)90188-x.
- 636 88. Jones ML, Evans N, Tefertiller C, Backus D, Sweatman M, Tansey K et al. Activity-
637 Based Therapy for Recovery of Walking in Individuals With Chronic Spinal Cord Injury:
638 Results From a Randomized Clinical Trial. *Arch Phys Med Rehabil*. 2014;95(12):2239-46.
639 doi:10.1016/j.apmr.2014.07.400.
- 640 89. Li J, Polston KFL, Eraslan M, Bickel CS, Windham ST, McLain AB et al. A high-
641 protein diet or combination exercise training to improve metabolic health in individuals with

- 642 long- standing spinal cord injury: a pilot randomized study. *Physiol Rep*. 2018;6(16).
 643 doi:10.14814/phy2.13813.
- 644 90. Thompson JD, Peacock AO, Betts AJ. Substitution and Compensation Erode the Energy
 645 Deficit from Exercise Interventions. *Med Sci Sports Exerc*. 2014;46(2):423-.
 646 doi:10.1249/MSS.0000000000000164.
- 647 91. Nightingale TE, Williams S, Thompson D, Bilzon JLJ. Energy balance components in
 648 persons with paraplegia: daily variation and appropriate measurement duration. *The*
 649 *international journal of behavioral nutrition and physical activity*. *Int J Behav Nutr Phys Act*.
 650 2017;14(1):132. doi:10.1186/s12966-017-0590-z.
- 651 92. Radziuk J. Homeostatic model assessment and insulin sensitivity/resistance. *Diabetes*.
 652 2014;63(6):1850. doi:10.2337/db14-0116.
- 653 93. Matsuda M, DeFronzo R. Insulin sensitivity indices obtained from oral glucose tolerance
 654 test: Comparison with the euglycemic insulin clamp. *Diabetes*. 1999;48:A79-A.
- 655 94. Gorgey AS, Graham ZA, Bauman WA, Cardozo C, Gater DR. Abundance in proteins
 656 expressed after functional electrical stimulation cycling or arm cycling ergometry training in
 657 persons with chronic spinal cord injury. *J Spinal Cord Med*. 2017;40(4):439-48.
 658 doi:10.1080/10790268.2016.1229397.
- 659 95. Mann S, Beedie C, Jimenez A. Differential Effects of Aerobic Exercise, Resistance
 660 Training and Combined Exercise Modalities on Cholesterol and the Lipid Profile: Review,
 661 Synthesis and Recommendations. *Sports Medicine*. 2014;44(2):211-21. doi:10.1007/s40279-
 662 013-0110-5.
- 663 96. Gilbert O, Croffoot JR, Taylor AJ, Nash M, Schomer K, Groah S. Serum lipid
 664 concentrations among persons with spinal cord injury - A systematic review and meta-
 665 analysis of the literature. *Atherosclerosis*. 2014;232(2):305-12.
 666 doi:10.1016/j.atherosclerosis.2013.11.028.

667 **Figure 1.** PRISMA flow diagram

The effect of exercise on cardiometabolic risk factors in adults with chronic spinal cord injury: A systematic review

ABSTRACT

Objective To determine the effects of exercise on individual cardiometabolic syndrome (CMS) risk factors in adults with chronic spinal cord injury (SCI).

Data sources English language searches of PubMed, Web of Science, EMBASE, and Scopus (01/01/1970 to 31/07/2019).

Study Selection Articles were included if they met the following criteria: (1) original articles with statistical analysis, (2) participants were adults with a SCI sustained \geq 1-year ago, (3) exercise intervention duration \geq 2 weeks, and (4) included any CMS risk factor as an outcome.

Data Extraction The methodological quality of articles was assessed using the Downs and Black score.

Data Synthesis Sixty-five studies were included for the final analysis, including nine studies classified as high quality ($\geq 66\%$), 35 studies classified as fair quality (50-66%), and 21 studies classified as low quality ($< 50\%$). Improvements in waist circumference (4/6 studies) and markers of hepatic insulin sensitivity (4/5 studies) were reported following upper-body aerobic exercise training, but no improvements in fasting glucose (8/8 studies), lipid profile (6/8 studies), systolic (8/9 studies) or diastolic blood pressure (9/9 studies) were observed. Improvements in markers of peripheral insulin sensitivity (5/6 studies) were observed following functional electrical stimulation (FES)-cycling. Improvements in lipid profile (4/5 studies) were observed following upper-body resistance training (RT) (with or without aerobic exercise). No consistent improvements in CMS risk factors were observed following assisted ambulation, FES-hybrid, FES-rowing, and FES-RT.

Conclusions Upper-body aerobic exercise training (>75% maximum heart rate) appears to improve waist circumference and hepatic insulin sensitivity, but appears insufficient for improving fasting glucose, lipid profile, or resting blood pressure. The addition of RT to upper-body aerobic exercise may elicit favourable changes in the lipid profile. More high-quality studies are needed to confirm if FES-cycling is effective at improving peripheral insulin sensitivity.

Key Words spinal cord injuries, exercise therapy, metabolic diseases

Abbreviations

CMS cardiometabolic syndrome

DBP diastolic blood pressure

ES effect size

FES functional electrical stimulation

HDL-C high-density lipoprotein-cholesterol

HOMA-IR homeostatic model assessment insulin resistance

HRR heart rate reserve

ISI-matsuda insulin sensitivity index

LDL-C low-density lipoprotein-cholesterol

RT resistance training

RCT randomised controlled trial

SBP systolic blood pressure

SCI spinal cord injury

TC total cholesterol

TG triglycerides

Persons with a spinal cord injury (SCI) are at an increased risk of cardiovascular disease and diabetes compared to able-bodied individuals [1, 2]. The risk of developing these chronic diseases is raised in individuals who present with a clustering of associated risk factors including: obesity, insulin resistance, dyslipidaemia, and hypertension, or as commonly referred to, cardiometabolic syndrome (CMS) [3]. The International Diabetes Federation defines CMS as central obesity (indicated by waist circumference), plus the presence (or treatment) of two of more of the following: hypertriglyceridemia (≥ 1.7 mmol/L), reduced high-density lipoprotein-cholesterol (HDL-C) (< 1.03 mmol/L for men, < 1.29 mmol/L for women), hypertension (systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 85 mmHg), and raised fasting plasma glucose (≥ 5.6 mmol/L, or diagnosed with type 2 diabetes) [4]. A waist circumference greater than 94 cm and/or a body mass index of greater than 22 kg/m^2 have been suggested as suitable cut-points to define central obesity in SCI [5, 6]. The prevalence of CMS in chronic SCI appears to be high; with the largest study to date ($n=473$) reporting a prevalence rate of 57.5% [7].

There is strong evidence that exercise is an effective countermeasure for the prevention of chronic disease and the treatment of CMS risk factors in the able-bodied population [8]. This has allowed national and global health organisations to produce guidelines regarding the total volume and intensity of physical activity (minimum of 150 min/week of moderate-intensity, or 75 minutes/week of vigorous-intensity) required to improve cardiometabolic health [9, 10]. However, as the most recent systematic review of the effect of exercise on health in SCI concluded, the evidence base for spinal cord injured persons “lags far behind” that for the general population [11]. This review formed the basis for the latest SCI-exercise guidelines, which recommend adults with a chronic SCI perform a minimum of 90 min/week of moderate-to-vigorous intensity aerobic exercise to improve cardiometabolic health [12]. Additional systematic reviews have also reported beneficial effects of exercise on specific CMS risk

factors, including systemic inflammation (C - reactive protein) and obesity (fat mass and waist circumference) in persons with chronic SCI [13, 14].

Since the last systematic search of the literature by van der Scheer and colleagues (search date: 1st Jan 2016), several randomised controlled trials assessing the effect of exercise training on CMS risk factors in SCI have been published. However, this systematic review did not address clinical thresholds for CMS risk factors at baseline, the magnitude of change following exercise training, and how different exercise modalities may impact specific individual CMS biomarkers. These questions are important for practitioners prescribing exercise to patients presenting with CMS risk factors, and researchers designing future studies in this field. A review which addresses these importance issues and focuses specifically on how different forms of exercise impacts on individual CMS risk factors in chronic SCI is therefore required. The aim of this systematic review is to determine the effect of different exercise modality interventions on CMS risk factors in adults with chronic SCI.

METHODS

The study inclusion criteria and planned analysis were specified in advance (PROSPERO:CRD42018105110) and the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed [15]. The databases of PubMed, Web of Science, EMBASE, and Scopus (Elsevier) were searched on 22nd August 2018, using a search strategy formulated based on a similar previous systematic review [11]. The search was repeated on 31st July 2019 to identify any additional articles prior to publication. The search strategy was piloted to ensure known articles were included and reviewed by two authors (MF & TN). The full search strategy for PubMed is presented in Supplement 1 as an exemplar. Briefly, the search was performed by combining key words associated with SCI (e.g., “paraplegia”, “spinal cord lesion”), exercise, (e.g., “physical activity”, “resistance training”,

“functional electrical stimulation”) and CMS risk factors (e.g., “glucose”, “BMI”, “blood pressure”). The reference list of included items and previous systematic reviews were checked and further articles identified. The final step involved hand-searching the journals which had returned the highest proportion of articles in the initial search, to identify any additional studies (e.g. Journal of Spinal Cord Medicine (1982-2018) and Archives of Physical Medicine and Rehabilitation (1985-2018)).

Titles and abstracts of retrieved articles were independently screened for relevance by two reviewers (MF & TN). The same two reviewers independently assessed the full text of relevant articles for eligibility. In the event of any disagreements in article selection, a third reviewer (JB) made the final decision. Articles were included if they met the criteria according to the PICOS structure: i) *participants* - $\geq 50\%$ of participants were aged ≥ 18 years old, and had a chronic SCI (≥ 1 year post-injury), ii) *intervention* - included an exercise training programme (any, or combination of: voluntary upper-body exercise, lower-body functional electrical stimulation (FES), and assisted ambulation training) lasting ≥ 2 weeks, iii) *comparison* – studies comparing exercise intervention to a control group or pre-intervention data, iv) *outcomes* - study included at least one CMS risk factor as an outcome variable (see Table 1) [4], and v) *study design* - study employed and reported quantitative statistical analysis to determine the impact of the exercise intervention on the relevant CMS risk outcome(s) (i.e. case reports and case-series were excluded), and was published in an English-language peer-reviewed journal (i.e. abstracts and conference proceedings were excluded) between 1st January 1970 and the final search date. Studies involving solely neuromuscular electrical stimulation (NMES) with no functional movement and passive cycling were excluded on the basis that the skeletal muscle contractions produced during these activities do not directly produce a functional movement, and therefore cannot be classed as exercise, *per se*. Studies assessing the impact of exercise on solely blood pressure amongst tetraplegics were excluded on the basis that the aim

of the exercise intervention was to increase resting blood pressure, and therefore was not reflective of a CMS risk factor (i.e. hypertension).

Two articles did not identify participants' time since injury [16, 17]. The corresponding authors were contacted by email and asked to provide clarification and given two weeks to respond. Both articles were excluded as the corresponding authors were unable to provide this information.

Two reviewers (MF and JM) independently evaluated the quality of included studies using a modified Downs and Black scale [18]. In the modified version, the scoring for question 27 (relating to statistical power) is simplified to "Yes" (1) or "No" (0). In the event of any discrepancies in scoring, discussion between the reviewers was used to reach a consensus. The total Downs & Black score for each article was expressed as a percentage of the maximum score possible (28) to allow categorisation of study quality [19]. Articles were classified as high ($\geq 66.7\%$), fair (between 50.0% and 66.6%), or low ($< 50.0\%$) quality [19].

An insufficient number of studies examined the same outcomes following similar exercise modalities, precluding a meta-analysis. Therefore, a coding system [19] was used to summarise the effect of different exercise training modalities on each CMS risk factor (Table 2). If 0-33% of studies reported a statistically significant change in a specific CMS risk factor following exercise training, the result was categorised as 'no effect'. If 34-59% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as 'inconsistent'. If 60-100% of studies reported a statistically significant change in a CMS risk factor following exercise training, the result was categorised as 'positive'. If four or more studies reported the same effect, the result was highlighted in bold to indicate a consistent finding. The findings from one particular study [20] were counted as non-significant for summary coding, due to the significance being set at $p < 0.10$, with actual p

values not reported. Data extraction was performed by MF, and later checked independently by TN, JM, and JB.

To aid interpretation of results, group average values at baseline for body mass index ($\geq 22 \text{ kg/m}^2$) [6], waist circumference ($> 94 \text{ cm}$) [5], triglycerides (TG) ($\geq 1.7 \text{ mmol/L}$), total cholesterol (TC) ($\geq 5 \text{ mmol/L}$), low-density lipoprotein (LDL-C) ($> 3 \text{ mmol/L}$), HDL-C ($< 1.03 \text{ mmol/L}$), fasting glucose ($\geq 5.6 \text{ mmol/L}$), systolic blood pressure (SBP) ($\geq 130 \text{ mmHg}$), and diastolic blood pressure (DBP) ($\geq 85 \text{ mmHg}$) [4] were highlighted to indicate that they can be classified as clinically high, according to the International Diabetes Federation and SCI-specific guidelines (Tables 3-9).

The terms hepatic insulin sensitivity and peripheral insulin sensitivity are used throughout this systematic review. Hepatic insulin sensitivity refers to insulin sensitivity in the fasted state and is measured by variables such as fasting insulin and/or glucose concentration and integrated indices such as HOMA-IR. Peripheral insulin sensitivity refers to insulin-mediated skeletal muscle glucose disposal and is usually measured by looking at blood glucose and insulin in responses to an oral glucose challenge (e.g. oral glucose tolerance test) and categorized using indices such as ISI-matsuda.

RESULTS

The initial database search yielded a total of 2450 unique records, of which 2245 were excluded following title and abstract screening. An additional 10 articles were retrieved from; hand-searching of relevant journals ($n=1$), relevant systematic reviews ($n=2$), the associated reference list of an included paper ($n=4$), and the updated search ($n=3$). Therefore, the full-text of 215 studies were subsequently assessed, three papers [21-23] contained data presented in another article, and these were removed from all analysis, leaving 65 articles for final review. The study selection process is detailed in Figure 1.

There was substantial agreement between reviewers for title and abstract screening ($k=0.635$, 95% CI: 0.581, 0.689), and almost perfect agreement for the full-text screening ($k=0.880$, 95% CI: 0.811, 0.949) [24].

We identified studies as pre-post designs ($n=47$), RCTs ($n=15$), non-randomised controlled trials ($n=2$), and a retrospective cohort study ($n=1$). Numerous studies utilised arm-cranking ($n=9$), wheelchair ergometry ($n=3$), wheelchair treadmill propulsion ($n=2$), or hand-cycling ($n=2$). These 16 studies were grouped together for analysis as voluntary upper-body aerobic exercise (Table 3). Seven studies utilised upper-body resistance training (RT) (with or without upper-body aerobic exercise) (Table 4). The most common exercise modality was FES-cycling ($n=17$) (Table 5). Six studies utilised FES-resistance training (FES-RT) exercise (in the form of non-isometric knee extensions), and three studies involved a combination of FES-cycling and FES-RT (Table 6). Studies which involved hybrid functional electrical stimulation (FES)-cycling ($n=4$) or FES-rowing ($n=4$) were grouped together as they both involve lower-body FES combined with voluntary upper-body aerobic exercise (Table 7). Several studies utilised solely body weight supported treadmill training ($n=6$), FES-walking, exoskeletal body weight supported treadmill training ($n=1$), or robotic body weight supported treadmill training ($n=1$). These 10 studies were grouped together for analysis (Table 8). Studies that involved a combination of upper-body aerobic, upper-body RT and neuromuscular stimulation ($n=1$), or a combination of lower-body FES-RT, and BWSTT ($n=1$), were not grouped for qualitative analysis (Table 9).

Intervention durations ranged from four to 52 weeks, with the most common length of 12 weeks ($n=14$). Training frequency ranged from 1 to 7 sessions per week, with three times per week the most common frequency of exercise performed ($n=35$). No serious adverse events were reported in any of the included studies.

Sample sizes ranged from four to 48. Only seven studies reported a-priori sample size calculations, and four of these met their target sample size (Table 10). There was a total of 872 participants (658 men, 110 women, 104 NR) (Table 10). There were nine studies classified as high quality, 35 studies classified as fair quality, and 21 studies classified as low quality. The most commonly assessed outcome measures for obesity, glycaemic control, dyslipidaemia, inflammation, vascular dysregulation, and thrombotic state were body mass (n=28), interleukin-6 (n=7), HDL-C (n=23), fasting glucose (n=18), PAI-1 (n=3), and systolic blood pressure (n=22), respectively. No studies reported outcome measures of hip circumference, liver fat content, apolipoprotein B, or proinsulin.

DISCUSSION

There are consistent findings that voluntary upper-body aerobic exercise ($>75\%$ HR_{MAX}) is effective in reducing waist circumference, and improving hepatic insulin sensitivity (i.e. fasting insulin concentration and HOMA-IR), however it does not appear to improve fasting glucose concentrations, lipid profile or resting blood pressure in persons with chronic SCI. The addition of upper-body RT appears to have an inconsistent effect on lipid profiles, but given the limited number of high-quality studies on combined exercise modalities, more research is needed in this area. FES-cycling may improve outcomes relating to peripheral insulin sensitivity (i.e. ability of the skeletal muscle to dispose of glucose), but more high-quality studies are required to strengthen the available evidence. There is insufficient evidence to conclude if FES-resistance training, FES-hybrid, FES-rowing, or assisted ambulation training improves any of these CMS risk factors.

Four [27, 25, 34, 33] of the six studies utilising upper-body aerobic exercise reported a reduction in supine waist circumference (-1.9 to -3.7 cm, ES: 0.26-2.67), indicating that this form of exercise is effective for reducing central obesity. A reduction in waist circumference (-2.5 cm) was achieved with as few as 64 min/week of exercise at 65-75% HRR [25], though this reduction did not translate to any change in android fat mass [25]. There was also no change in visceral adipose tissue [26] following 180 min/week at 60-65% $\dot{V}O_{2peak}$ of upper-body aerobic exercise. Future studies should combine both surrogate and gold-standard measures (i.e. DEXA/CT derived) of central obesity/adiposity to further elucidate changes in body composition. Given the relatively small skeletal muscle mass involved in upper-body aerobic exercise, it is perhaps unsurprising that there were consistent findings that body mass and BMI were unchanged, as reported in a previous systematic review [14]. Whilst not part of the search strategy, only one study in this category measured free-living energy intake and expenditure

during the exercise intervention [26]. In order to better understand the isolated impact of prescribed exercise interventions on energy balance and body composition, future studies should also attempt to estimate total energy intake and total energy expenditure. This would account for any compensatory changes in diet or exercise behaviours, providing a better understanding of the overall impact of exercise interventions on energy balance in SCI [90]. Guidelines for measuring these variables in persons with chronic SCI have been published elsewhere [91].

Four [25, 28, 26, 33] of the five studies that measured fasting insulin resistance by HOMA-IR and/or fasting insulin concentrations reported a reduction (22-40%, ES: 1.07-1.78) following upper-body aerobic exercise, suggesting that this form of exercise is effective at improving hepatic insulin sensitivity (i.e. ability of the liver to dispose of glucose). The single study [31] to find no statistically significant change in fasting insulin concentration following upper-body aerobic exercise, reported that all five participants had a lower insulin concentration (22-76%, ES: 0.41) post-training, indicating that the study simply lacked the statistical power to demonstrate an effect. Despite the improvement in hepatic insulin sensitivity [92] observed following upper-body aerobic exercise, the three studies [26, 28, 31] that measured outcomes relating to peripheral insulin sensitivity [93] found no changes following training. This is likely as a result of the limited skeletal muscle mass involved (i.e. limited sink for glucose disposal). Furthermore, the upper-body skeletal musculature is usually already well-conditioned from habitual wheelchair propulsion, meaning that moderate-intensity upper-body exercise is likely an insufficient stimulus to substantially promote molecular adaptations (e.g. GLUT4 translocation, mitochondrial biogenesis) associated with improved peripheral insulin sensitivity [94]. A high quality study reported no improvement in glucose or insulin area under the curve despite 180 min/week of exercise at 60-65% $\dot{V}O_{2peak}$ [26]. This suggests that even large volumes of upper-body aerobic exercise above the

recommended guidelines of 90 min/week [12] may be insufficient to improve markers of peripheral insulin sensitivity.

There are also numerous studies indicating that upper-body aerobic exercise alone does not improve fasting glucose, resting blood pressure (SBP, DBP), or lipid profiles (TC, HDL-C, LDL-C, and TG). All eight studies [25, 26, 28, 31-35] measuring fasting glucose reported no change following upper-body aerobic exercise. However, only one study [34] reported a clinically elevated group mean glucose concentration at baseline (≥ 5.6 mmol/L). Nine studies [29, 35, 38, 39, 25, 26, 34, 32, 31] measured changes in resting blood pressure following upper-body aerobic exercise. The only study [34] where participants presented with clinically elevated systolic blood pressure (≥ 130 mmHg) at baseline reported a reduction (3 mmHg, ES: 0.66) following 10 weeks of exercise training (4 sessions/week 50-70% HRR, 60 min). Thus, a basement effect may explain the lack of significant changes in fasting glucose and resting blood pressure in participants presenting with healthy values at baseline. Eight studies measured TG, TC, HDL-C, or LDL-C [25, 26, 28, 32-35, 20] following upper-body aerobic exercise, including four with clinically high mean concentrations at baseline. Only two studies reported a significant reduction in any variable. One study [34] reported a 25% reduction (ES: 0.31) in TG in participants with a clinically elevated mean concentrations at baseline (≥ 1.7 mmol/L). One study reported improvements in HDL-C, LDL-C, TC: HDL-C and TG following 60 mins/week at 70-80% HRR, however the threshold for significance was set at $p < 0.10$ [40]. It therefore appears that upper-body aerobic exercise may not be an adequate stimulus to improve blood lipid profile irrespective of baseline values. This is likely due to the low energy expenditure achieved through upper-body exercise, which appears to drive changes in the lipid profile [95].

Upper-body RT (with or without aerobic exercise) appears to reduce central obesity, with three [42-44] out of four studies reporting a reduction in waist circumference (-

1.0 to -2.6 cm) or waist to hip ratio (-0.02). These changes were accompanied by a decrease in whole-body fat mass and visceral adipose tissue following 120 min/week of training (3 x 10 of 50-70% 1RM, 20 min at 3-6 RPE) [42]. Upper-body RT (with or without aerobic exercise) may elicit improvements in lipid profile, with four [43-45, 40] out of the five retrieved studies reporting a beneficial effect of at least one marker (TC, HDL-C, LDL-C, TC: HDL-C, and TG). However, more studies are needed to determine this, particularly given the high-quality study reporting no change in the lipid profile following 16-weeks of twice-weekly combined training [42].

Five [50, 54, 58, 60, 62] of the six studies to measure outcomes relating to peripheral insulin sensitivity reported a significant improvement following FES-cycling. The largest of these studies (n=18) [54] reported a significant reduction in glucose and insulin at multiple time-points during a 2-h oral glucose tolerance test following 10 weeks of exercise (2-3 sessions/week, 30 min). However, four of these studies were rated as low quality, and therefore more high-quality studies are needed to confirm if FES-cycling can improve peripheral insulin sensitivity, which upper-body exercise appears unable to achieve. Surprisingly, we identified no RCT's assessing the efficacy of FES-cycling compared to a true control group (i.e. passive cycling or stretching), which should be addressed in future research. Four studies reported no change in body mass following FES-hybrid or FES-rowing training. There was a distinct lack of training studies with sufficient breadth of outcomes to make any other meaningful conclusions on the effect of FES-RT, FES-hybrid, FES-rowing and assisted ambulation on CMS risk factors. Nonetheless, given that hybrid training (2 sessions/week, 18-32 min, 65-75% HRR) [25] improved a multitude of CMS risk factors (waist circumference, android fat percentage, TG, DBP), and that different exercise modalities appear to offer specific benefits to CMS risk factors, other rigorously conducted prospective studies assessing multimodal (e.g.

FES-cycling combined with upper-body aerobic and resistance exercise) interventions should be conducted in this area of promise.

This review has highlighted the lack of research assessing novel markers of CMS risk, including outcomes relating to inflammation, DEXA/CT derived measures of central adiposity, and endothelial function. It is clear that many studies in the area recruit a convenience sample of relatively active and lean individuals, who are not reflective of the wider, chronic SCI population (i.e. poor metabolic health), which should be considered when interpreting results. For example, individuals with SCI have a significantly lower HDL-C compared to able-bodied controls (1.06 vs 1.28 mmol/L) [96], however only five of the 23 studies to measure HDL-C had a clinically low mean concentration at baseline (<1.03 mmol/L). As is widely acknowledged, this review has also confirmed the existing evidence base of exercise and CMS risk in SCI lacks sufficiently powered (four in total identified), high-quality studies (eight in total identified). However, this review identified 16 additional studies, published since the previous systematic review by van der Scheer and colleagues [11] that were all categorised as fair or high quality, including eight RCT's.

Study Limitations

The main limitation of this systematic review is the use of summary coding to draw conclusions regarding the effect of each exercise modality on specific CMS risk factors. Due to the variability in CMS risk factors measured, exercise modes and training parameters (i.e. exercise intensity and volume), and participant characteristics (i.e. paraplegic vs. tetraplegic), a meta-analysis was not possible. Whilst the coding system provides a useful assessment of the consistency of findings in the field, it uses arbitrary classifications and does not distinguish studies of differing quality. However, when studies rated as 'low-quality' were removed from this analysis (Supplement 3), the conclusions remained unchanged, with the exception of

331 potential of FES-cycling to improve peripheral insulin sensitivity. Further, given that the vast
332 majority of included studies lacked sufficient statistical power, there is a risk of a type II error
333 in the conclusions formed. Finally, this review did not include acute SCI as van der Scheer and
334 colleagues [11] determined there was an “absence of high-quality, consistent evidence” in this
335 area, a view which still appears to be true.

CONCLUSIONS

In summary, this systematic review has provided evidence that in adults with chronic SCI, upper-body aerobic exercise improves outcomes relating to central obesity and hepatic insulin sensitivity, but is not sufficient to improve fasting glucose, lipid profiles, or resting blood pressure. Practitioners should consider prescribing moderate-to-vigorous intensity (>75% HR_{MAX}) upper-body aerobic exercise to improve fasting glycaemic control and central obesity. To elicit improvements in lipid profile, this should be combined with upper-body resistance training. More high-quality randomised controlled trials assessing novel markers of CMS and responses to combined exercise interventions (e.g. aerobic exercise with resistance training), high-intensity exercise interventions, and FES-based exercise are needed to inform and refine evidence-based exercise guidelines for the prevention and management of CMS in this population.

REFERENCES

1. Cragg JJ, Noonan VK, Dvorak M, Krassioukov A, Mancini GB, Borisoff JF. Spinal cord injury and type 2 diabetes: results from a population health survey. *Neurology*. 2013;81(21):1864-8. doi:10.1212/01.wnl.0000436074.98534.6e.
2. Cragg JJ, Noonan VK, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury: results from a national population health survey. *Neurology*. 2013;81(8):723-8. doi:10.1212/WNL.0b013e3182a1aa68.
3. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med*. 2005;165(22):2644-50. doi:10.1001/archinte.165.22.2644.
4. Alberti K, Zimmet P, Shaw J. Metabolic syndrome - a new world-wide definition. A consensus statement from the international diabetes federation. *Diabetic Medicine*. 2006;23(5):469-80. doi:10.1111/j.1464-5491.2006.01858.x.
5. Ravensbergen HJC, Lear SA, Claydon VE. Waist Circumference Is the Best Index for Obesity-Related Cardiovascular Disease Risk in Individuals with Spinal Cord Injury. *Journal of Neurotrauma*. 2014;31(3):292-300. doi:10.1089/neu.2013.3042.
6. Laughton GE. Lowering body mass index cutoffs better identifies obese persons with spinal cord injury. *Spinal Cord*. 2009;47(10):757-63.
7. Gater DR, Farkas GJ, Berg AS, Castillo C. Prevalence of metabolic syndrome in veterans with spinal cord injury. *J Spinal Cord Med*. 2019; 42:86-93. doi:10.1080/10790268.2017.1423266.
8. Booth FW, Roberts CK, Laye MJ. Lack of Exercise Is a Major Cause of Chronic Diseases. *Compr Physiol*. 2012;2(2):1143-211. doi:10.1002/cphy.c110025.

- 372 9. Piercy K, Troiano R, Ballard RM, Carlson SA, Fulton J, Galuska D et al. The Physical
 373 Activity Guidelines for Americans. *J Am Med Assoc.* 2018;320(19):2020-8.
 374 doi:10.1001/jama.2018.14854.
- 375 10. WHO. Global recommendations on physical activity for health. 2010.
- 376 11. van der Scheer JW, Ginis KAM, Ditor DS, Goosey-Tolfrey VL, Hicks AL, West CR et
 377 al. Effects of exercise on fitness and health of adults with spinal cord injury A systematic
 378 review. *Neurology.* 2017;89(7):736-45. doi:10.1212/wnl.0000000000004224.
- 379 12. Ginis KAM, van der Scheer JW, Latimer-Cheung AE, Barrow A, Bourne C, Carruthers P
 380 et al. Evidence-based scientific exercise guidelines for adults with spinal cord injury: an
 381 update and a new guideline. *Spinal Cord.* 2018;56(4):308-21. doi:10.1038/s41393-017-0017-
 382 3.
- 383 13. Neefkes-Zonneveld CR, Bakkum AJ, Bishop NC, van Tulder MW, Janssen TW. Effect of
 384 Long-Term Physical Activity and Acute Exercise on Markers of Systemic Inflammation in
 385 Persons With Chronic Spinal Cord Injury: A Systematic Review. *Arch Phys Med Rehabil.*
 386 2015;96(1):30-42. doi:10.1016/j.apmr.2014.07.006.
- 387 14. Shojaei MH, Alavinia SM, Craven BC. Management of obesity after spinal cord injury: a
 388 systematic review. *J Spinal Cord Med* 2017;40(6):783-94.
 389 doi:10.1080/10790268.2017.1370207.
- 390 15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA et al. The
 391 PRISMA statement for reporting systematic reviews and meta-analyses of studies that
 392 evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;339.
 393 doi:10.1136/bmj.b2700.
- 394 16. El-Sayed MS, Younesian A. Lipid profiles are influenced by arm cranking exercise and
 395 training in individuals with spinal cord injury. *Spinal Cord.* 2005;43(5):299-305.
 396 doi:10.1038/sj.sc.3101698.

- 397 17. Petrofsky JS, Stacy R. The effect of training on endurance and the cardiovascular
398 responses of individuals with paraplegia during dynamic exercise induced by functional
399 electrical stimulation. *Eur J Appl Physiol Occup Physiol*. 1992;64(6):487-92.
- 400 18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the
401 methodological quality both of randomised and non-randomised studies of health care
402 interventions. *J Epidemiol Community Health*. 1998;52(6):377-84.
403 doi:10.1136/jech.52.6.377.
- 404 19. Batacan RB, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high- intensity
405 interval training on cardiometabolic health: a systematic review and meta-analysis of
406 intervention studies. *Br J Sports Med*. 2017; 51: 494-503. doi:10.1136/bjsports-2015-095841.
- 407 20. Hooker SP, Wells CL. Effects of low- and moderate-intensity training in spinal cord-
408 injured persons. *Med Sci Sports Exerc*. 1989;21(1):18-22.
- 409 21. Ordonez FJ, Rosety MA, Camacho A, Rosety I, Diaz AJ, Fornieles G et al. Arm-cranking
410 exercise reduced oxidative damage in adults with chronic spinal cord injury. *Arch Phys Med*
411 *Rehabil*. 2013;94(12):2336-41. doi:10.1016/j.apmr.2013.05.029.
- 412 22. Rosety-Rodriguez M, Rosety I, Fornieles G, Rosety JM, Elosegui S, Rosety MA et al. A
413 short-term arm-crank exercise program improved testosterone deficiency in adults with
414 chronic spinal cord injury. *International Braz J Urol*. 2014;40(3):367-72. doi:10.1590/s1677-
415 5538.ibju.2014.03.10.
- 416 23. Willoughby DS, Priest JW, Nelson M. Expression of the stress proteins, ubiquitin, heat
417 shock protein 72, and myofibrillar protein content after 12 weeks of leg cycling in persons
418 with spinal cord injury. *Arch Phys Med Rehabil*. 2002;83(5):649-54.
419 doi:10.1053/apmr.2002.31184.
- 420 24. Sim J. The Kappa Statistic in Reliability Studies: Use, Interpretation, and Sample Size
421 Requirements. *Physical Therapy*. 2005;85(3):257-69.

- 422 25. Bakkum AJ, Paulson TA, Bishop NC, Goosey-Tolfrey VL, Stolwijk-Swuste JM, van
423 Kuppevelt DJ et al. Effects of hybrid cycle and handcycle exercise on cardiovascular disease
424 risk factors in people with spinal cord injury: A randomized controlled trial. *J Rehabil Med*.
425 2015;47(6):523-30. doi:10.2340/16501977-1946.
- 426 26. Nightingale TE, Walhin JP, Thompson D, Bilzon JLJ. Impact of Exercise on
427 Cardiometabolic Component Risks in Spinal Cord-injured Humans. *Med Sci Sports Exerc*.
428 2017;49(12):2469-77. doi:10.1249/mss.0000000000001390.
- 429 27. Rosety-Rodriguez M, Camacho A, Rosety I, Fornieles G, Rosety MA, Diaz AJ et al.
430 Low-Grade Systemic Inflammation and Leptin Levels Were Improved by Arm Cranking
431 Exercise in Adults With Chronic Spinal Cord Injury. *Arch Phys Med Rehabil*.
432 2014;95(2):297-302. doi:10.1016/j.apmr.2013.08.246.
- 433 28. Bresnahan JJ, Farkas GJ, Clasey JL, Yates JW, Gater DR. Arm crank ergometry improves
434 cardiovascular disease risk factors and community mobility independent of body composition
435 in high motor complete spinal cord injury. *J Spinal Cord Med*. 2018; 42(3): 272-80.
436 doi:10.1080/10790268.2017.1412562.
- 437 29. Han DS, Hsiao MY, Wang TG, Chen SY, Yang WS. Association of serum myokines and
438 aerobic exercise training in patients with spinal cord injury: An observational study. *BMC*
439 *Neurology*. 2016;16(1). doi:10.1186/s12883-016-0661-9.
- 440 30. McLean KP, Skinner JS. Effect of body training position on outcomes of an aerobic
441 training study on individuals with quadriplegia. *Arch Phys Med Rehabil*. 1995;76(2):139-50.
442 doi:10.1016/S0003-9993(95)80023-9.
- 443 31. Gorgey AS, Graham ZA, Bauman WA, Cardozo C, Gater DR. Abundance in proteins
444 expressed after functional electrical stimulation cycling or arm cycling ergometry training in
445 persons with chronic spinal cord injury. *J Spinal Cord Med*. 2017;40(4):439-48.
446 doi:10.1080/10790268.2016.1229397.

32. Akkurt H, Karapolat HU, Kirazli Y, Kose T. The effects of upper extremity aerobic exercise in patients with spinal cord injury: A randomized controlled study. *Eur J Phys Rehabil Med.* 2017;53(2):219-27. doi:10.23736/s1973-9087.16.03804-1.
33. Kim DI, Lee H, Lee BS, Kim J, Jeon JY. Effects of a 6-Week Indoor Hand-Bike Exercise Program on Health and Fitness Levels in People With Spinal Cord Injury: A Randomized Controlled Trial Study. *Arch Phys Med Rehabil.* 2015;96(11):2033-U325. doi:10.1016/j.apmr.2015.07.010.
34. Horiuchi M, Okita K. Arm-Cranking Exercise Training Reduces Plasminogen Activator Inhibitor 1 in People With Spinal Cord Injury. *Arch Phys Med Rehabil.* 2017;98(11):2174-80. doi:10.1016/j.apmr.2017.02.007.
35. Midha M, Schmitt JK, Sclater M. Exercise effect with the wheelchair aerobic fitness trainer on conditioning and metabolic function in disabled persons: A pilot study. *Arch Phys Med Rehabil.* 1999;80(3):258-61. doi:10.1016/s0003-9993(99)90135-1.
36. Mukherjee G, Bhowmik P, Samanta A. Physical fitness training for wheelchair ambulation by the arm crank propulsion technique. *Clin Rehabil.* 2001;15(2):125-32. doi:10.1191/026921501666069173.
37. Gass GC, Watson J, Camp EM, Court HJ, McPherson LM, Redhead P. The effects of physical training on high level spinal lesion patients. *Scand J Rehabil Med.* 1980;12(2):61.
38. Yim SY, Cho KJ, Park CI, Yoon TS, Han DY, Kim SK et al. Effect of wheelchair ergometer training on spinal cord-injured paraplegics. *Yonsei Med. J.* 1993;34(3):278-86. doi:10.3349/ymj.1993.34.3.278.
39. Davis GM, Shephard RJ, Leenen FH. Cardiac effects of short term arm crank training in paraplegics: echocardiographic evidence. *Eur J Appl Physiol Occup Physiol.* 1987;56(1):90-6.

- 471 40. Hooker SP, Wells CL. Effects of low- and moderate-intensity training in spinal cord-
 472 injured persons. *Med Sci Sports Exerc.* 1989;21(1):18-22. doi:10.1249/00005768-
 473 198902000-00004.
- 474 41. Giangregorio L, Craven C, Richards K, Kapadia N, Hitzig SL, Masani K et al. A
 475 randomized trial of functional electrical stimulation for walking in incomplete spinal cord
 476 injury: Effects on body composition. *J Spinal Cord Med.* 2012;35(5):351-60.
 477 doi:10.1179/2045772312y.0000000041.
- 478 42. de Zepetnek JOT, Pelletier CA, Hicks AL, MacDonald MJ. Following the Physical
 479 Activity Guidelines for Adults With Spinal Cord Injury for 16 Weeks Does Not Improve
 480 Vascular Health: A Randomized Controlled Trial. *Arch Phys Med Rehabil.* 2015;96(9):1566-
 481 75. doi:10.1016/j.apmr.2015.05.019.
- 482 43. Mogharnasi M, TaheriChadorneshin H, Papoli-Baravati SA, Teymuri A. Effects of upper-
 483 body resistance exercise training on serum nesfatin-1 level, insulin resistance, and body
 484 composition in obese paraplegic men. *Disabil Health J.* 2019; 12(1): 29-34.
 485 doi:10.1016/j.dhjo.2018.07.003.
- 486 44. Kim D-I, Taylor JA, Tan CO, Park H, Kim JY, Park S-Y et al. A pilot randomized
 487 controlled trial of 6-week combined exercise program on fasting insulin and fitness levels in
 488 individuals with spinal cord injury. *Eur Spine J.* 2019; 28(5); 1082-1091.
 489 doi:10.1007/s00586-019-05885-7.
- 490 45. Cugusi L, Solla P, Serpe R, Pilia K, Pintus V, Madeddu C et al. Effects of an adapted
 491 physical training on functional status, body composition and quality of life in persons with
 492 spinal cord injury paraplegia: a pilot study. *Med Sport (Roma).* 2015;68(3):473-85.
- 493 46. Hicks AL, Adams MM, Martin Ginis K, Giangregorio L, Latimer A, Phillips SM et al.
 494 Long-term body-weight-supported treadmill training and subsequent follow-up in persons

- 495 with chronic SCI: effects on functional walking ability and measures of subjective well-
 496 being. *Spinal Cord*. 2005;43(5):291-8. doi:10.1038/sj.sc.3101710.
- 497 47. Nash MS, Jacobs PL, Mendez AJ, Goldberg RB. Circuit resistance training improves the
 498 atherogenic lipid profiles of persons with chronic paraplegia. *J Spinal Cord Med*.
 499 2001;24(1):2-9.
- 500 48. Allison DJ, Chapman B, Wolfe D, Sequeira K, Hayes K, Ditor DS. Effects of a functional
 501 electrical stimulation-assisted cycling program on immune and cardiovascular health in
 502 persons with spinal cord injury. *Top Spinal Cord Inj Rehabil*. 2016;22(1):71-8.
 503 doi:10.1310/sci2201-71.
- 504 49. Sadowsky CL, Hammond ER, Strohl AB, Commean PK, Eby SA, Damiano DL et al.
 505 Lower extremity functional electrical stimulation cycling promotes physical and functional
 506 recovery in chronic spinal cord injury. *J Spinal Cord Med*. 2013;36(6):623-31.
 507 doi:10.1179/2045772313Y.00000000101.
- 508 50. Jeon JY, Weiss CB, Steadward RD, Ryan E, Burnham RS, Bell G et al. Improved glucose
 509 tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with
 510 spinal cord injury. *Spinal Cord*. 2002;40(3):110-7. doi:10.1038/sj/sc/3101260.
- 511 51. Gerrits HL. Peripheral vascular changes after electrically stimulated cycle training in
 512 people with spinal cord injury. *Arch Phys Med Rehabil*. 2001;82(6):832-40.
- 513 52. Liu CW, Chen SC, Chen CH, Chen TW, Chen JJ, Lin CS et al. Effects of functional
 514 electrical stimulation on peak torque and body composition in patients with incomplete spinal
 515 cord injury. *Kaohsiung J Med Sci*. 2007;23(5):232-40.
- 516 53. Faghri PD, Glaser RM, Figoni SF. Functional electrical stimulation leg cycle ergometer
 517 exercise: training effects on cardiorespiratory responses of spinal cord injured subjects at rest
 518 and during submaximal exercise. *Arch Phys Med Rehabil*. 1992;73(11):1085-93.

- 519 54. Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z et al. Functional electrical
520 stimulation cycling improves body composition, metabolic and neural factors in persons with
521 spinal cord injury. *J Electromyogr Kinesiol.* 2009;19(4):614-22.
522 doi:10.1016/j.jelekin.2008.03.002.
- 523 55. Robergs RA, Appenzeller O, Qualls C, Aisenbrey J, Krauss J, Kopriva L et al. Increased
524 endothelin and creatine kinase after electrical stimulation of paraplegic muscle. *J Appl*
525 *Physiol.* 1993;75(6):2400-5. doi:10.1152/jappl.1993.75.6.2400.
- 526 56. Hjeltne N, Aksnes AK, Birkeland KI, Johansen J, Lannem A, WallbergHenriksson H.
527 Improved body composition after 8 wk of electrically stimulated leg cycling in tetraplegic
528 patients. *Am J Physiol Regul Integr Comp Physiol.* 1997;273(3):R1072-R9.
- 529 57. Kahn NN, Feldman SP, Bauman WA. Lower-Extremity Functional Electrical Stimulation
530 Decreases Platelet Aggregation and Blood Coagulation in Persons With Chronic Spinal Cord
531 Injury: A Pilot Study. *J Spinal Cord Med.* 2010;33(2):150-8.
532 doi:10.1080/10790268.2010.11689690.
- 533 58. Hjeltne N, Galuska D, Bjornholm M, Aksnes AK, Lannem A, Zierath JR et al. Exercise-
534 induced overexpression of key regulatory proteins involved in glucose uptake and
535 metabolism in tetraplegic persons: molecular mechanism for improved glucose homeostasis.
536 *FASEB J.* 1998;12(15):1701-12.
- 537 59. Lammers G, Van Duijnhoven NTL, Hoenderop JG, Horstman AM, De Haan A, Janssen
538 TWJ et al. The identification of genetic pathways involved in vascular adaptations after
539 physical deconditioning versus exercise training in humans. *Exp Physiol.* 2013;98(3):710-21.
540 doi:10.1113/expphysiol.2012.068726.
- 541 60. Mohr T, Dela F, Handberg A, Biering-Sorensen F, Galbo H, Kjaer M. Insulin action and
542 long-term electrically induced training in individuals with spinal cord injuries. *Med Sci*
543 *Sports Exerc.* 2001;33(8):1247-52. doi:10.1097/00005768-200108000-00001.

- 544 61. Sköld C, Lönn L, Harms-Ringdahl K, Hultling C, Levi R, Nash M et al. Effects of
545 functional electrical stimulation training for six months on body composition and spasticity in
546 motor complete tetraplegic spinal cord-injured individuals. *J Rehabil Med.* 2002;34(1):25-32.
547 doi:10.1080/165019702317242677.
- 548 62. Chilibeck PD, Bell G, Jeon J, Weiss CB, Murdoch G, MacLean I et al. Functional
549 electrical stimulation exercise increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle.
550 *Metabolism.* 1999;48(11):1409-13. doi:10.1016/s0026-0495(99)90151-8.
- 551 63. Gorgey AS, Khalil R, Gill RS, Gater DR, Lavis TR, Cardozo C et al. Low-Dose
552 Testosterone and Evoked Resistance Exercise after Spinal Cord Injury TEREX-SCI on
553 Cardio-metabolic Risk Factors: An open-label randomized clinical trial. *J of Neurotrauma.*
554 2019. doi:10.1089/neu.2018.6136.
- 555 64. Gorgey AS, Mather KJ, Cupp HR, Gater DR. Effects of Resistance Training on Adiposity
556 and Metabolism after Spinal Cord Injury. *Med Sci Sports Exerc.* 2012;44(1):165-74.
557 doi:10.1249/MSS.0b013e31822672aa.
- 558 65. Rodgers MM, Glaser RM, Figoni SF, Hooker SP, Ezenwa BN, Collins SR et al.
559 Musculoskeletal responses of spinal cord injured individuals to functional neuromuscular
560 stimulation-induced knee extension exercise training. *J Rehabil Res Dev.* 1991;28(4):19-26.
- 561 66. Ryan TE, Brizendine JT, Backus D, McCully KK. Electrically Induced Resistance
562 Training in Individuals With Motor Complete Spinal Cord Injury. *Arch Phys Med Rehabil.*
563 2013;94(11):2166-73. doi:10.1016/j.apmr.2013.06.016.
- 564 67. Stoner L, Sabatier MJ, Mahoney ET, Dudley GA, McCully KK. Electrical stimulation-
565 evoked resistance exercise therapy improves arterial health after chronic spinal cord injury.
566 *Spinal Cord.* 2007;45(1):49-56. doi:10.1038/sj.sc.3101940.

- 567 68. Ragnarsson KT, Pollack S, O'Daniel Jr W, Edgar R, Petrofsky J, Nash MS. Clinical
568 evaluation of computerized functional electrical stimulation after spinal cord injury: A
569 multicenter pilot study. *Arch Phys Med Rehabil.* 1988;69(9):672-7.
- 570 69. Pollack SF, Axen K, Spielholz N, Levin N, Haas F, Ragnarsson KT. Aerobic training
571 effects of electrically induced lower extremity exercises in spinal cord injured people. *Arch*
572 *Phys Med Rehabil.* 1989;70(3):214-9.
- 573 70. Mahoney ET, Bickel CS, Elder C, Black C, Slade JM, Apple D et al. Changes in skeletal
574 muscle size and glucose tolerance with electrically stimulated resistance training in subjects
575 with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2005;86(7):1502-4.
576 doi:10.1016/j.apmr.2004.12.021.
- 577 71. Pacy PJ, Hesp R, Halliday DA, Katz D, Cameron G, Reeve J. Muscle and bone in
578 paraplegic patients, and the effect of functional electrical stimulation. *Clin Sci (Lond).*
579 1988;75(5):481-7.
- 580 72. Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training
581 and detraining in persons with spinal cord injury. *Arch Phys Med Rehabil.* 2006;87(4):474-
582 81. doi:10.1016/j.apmr.2005.11.005.
- 583 73. Kim DI, Park DS, Lee BS, Jeon JY. A six-week motor-driven functional electronic
584 stimulation rowing program improves muscle strength and body composition in people with
585 spinal cord injury: a pilot study. *Spinal Cord.* 2014;52(8):621-4. doi:10.1038/sc.2014.76.
- 586 74. Qiu S, Alzhab S, Picard G, Taylor JA. Ventilation Limits Aerobic Capacity after
587 Functional Electrical Stimulation Row Training in High Spinal Cord Injury. *Med Sci Sports*
588 *Exerc.* 2016;48(6):1111-9.
- 589 75. Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular
590 adaptations after hybrid training in spinal cord-injured subjects. *Med Sci Sports Exerc.*
591 2005;37(7):1112-8.

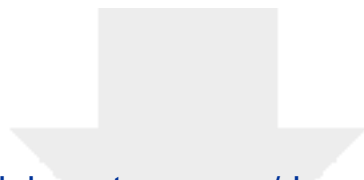
- 592 76. Wilbanks SR, Rogers R, Pool S, Bickel CS. Effects of functional electrical stimulation
593 assisted rowing on aerobic fitness and shoulder pain in manual wheelchair users with spinal
594 cord injury. *J Spinal Cord Med*. 2016;39(6):645-54. doi:10.1179/2045772315Y.00000000052.
- 595 77. Jeon JY, Hettinga D, Steadward RD, Wheeler GD, Bell G, Harber V. Reduced Plasma
596 Glucose and Leptin After 12 Weeks of Functional Electrical Stimulation-Rowing Exercise
597 Training in Spinal Cord Injury Patients. *Arch Phys Med Rehabil*. 2010;91(12):1957-9.
598 doi:10.1016/j.apmr.2010.08.024.
- 599 78. Hasnan N, Engkasan JP, Husain R, Davis GM. High-intensity virtual-reality arm plus
600 FES-leg interval training in individuals with spinal cord injury. *Biomed Tech (Berl)*.
601 2013;58(SUPPL. 1 TRACK-A). doi:10.1515/bmt-2013-4028
- 602 79. Gorman PH, Scott W, York H, Theyagaraj M, Price-Miller N, McQuaid J et al.
603 Robotically assisted treadmill exercise training for improving peak fitness in chronic motor
604 incomplete spinal cord injury: A randomized controlled trial. *J Spinal Cord Med*.
605 2016;39(1):32-44. doi:10.1179/2045772314y.00000000281.
- 606 80. Ditor DS, MacDonald MJ, Kamath MV, Bugaresti J, Adams M, McCartney N et al. The
607 effects of body-weight supported treadmill training on cardiovascular regulation in
608 individuals with motor-complete SCI. *Spinal Cord*. 2005;43(11):664-73.
609 doi:10.1038/sj.sc.3101785.
- 610 81. Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N, Hicks AL. Effects of
611 body weight-supported treadmill training on heart rate variability and blood pressure
612 variability in individuals with spinal cord injury. *J Appl Physiol*. 2005;98(4):1519-25.
613 doi:10.1152/jappphysiol.01004.2004.
- 614 82. Turiel M, Sitia S, Cicala S, Magagnin V, Bo I, Porta A et al. Robotic treadmill training
615 improves cardiovascular function in spinal cord injury patients. *Int J Cardiol*.
616 2011;149(3):323-9. doi:10.1016/j.ijcard.2010.02.010.

- 617 83. Giangregorio LM, Webber CE, Phillips SM, Hicks AL, Craven BC, Bugaresti JM et al.
 618 Can body weight supported treadmill training increase bone mass and reverse muscle atrophy
 619 in individuals with chronic incomplete spinal cord injury? *Appl Physiol Nutr Metab*.
 620 2006;31(3):283-91. doi:10.1139/h05-036.
- 621 84. Karelis AD, Carvalho LP, Castillo MJ, Gagnon DH, Aubertin-Leheudre M. Effect on
 622 body composition and bone mineral density of walking with a robotic exoskeleton in adults
 623 with chronic spinal cord injury. *J Rehabil Med*. 2017;49(1):84-7. doi:10.2340/16501977-
 624 2173.
- 625 85. Stewart BG, Tarnopolsky MA, Hicks AL, McCartney N, Mahoney DJ, Staron R et al.
 626 Treadmill training-induced adaptations in muscle phenotype in persons with incomplete
 627 spinal cord injury. *Muscle & Nerve*. 2004;30(1):61-8. doi:10.1002/mus.20046.
- 628 86. Phillips SM, Stewart BG, Mahoney DJ, Hicks AL, McCartney N, Tang JE et al. Body-
 629 weight-support treadmill training improves blood glucose regulation in persons with
 630 incomplete spinal cord injury. *J Appl Physiol*. 2004;97(2):716-24.
 631 doi:10.1152/jappphysiol.00167.2004.
- 632 87. Klose KJ, Jacobs PL, Broton JG, Guest RS, NeedhamShropshire BM, Lebowhl N et al.
 633 Evaluation of a training program for persons with SCI paraplegia using the Parastep(R)1
 634 ambulation system .1. Ambulation performance and anthropometric measures. *Arch Phys*
 635 *Med Rehabil*. 1997;78(8):789-93. doi:10.1016/s0003-9993(97)90188-x.
- 636 88. Jones ML, Evans N, Tefertiller C, Backus D, Sweatman M, Tansey K et al. Activity-
 637 Based Therapy for Recovery of Walking in Individuals With Chronic Spinal Cord Injury:
 638 Results From a Randomized Clinical Trial. *Arch Phys Med Rehabil*. 2014;95(12):2239-46.
 639 doi:10.1016/j.apmr.2014.07.400.
- 640 89. Li J, Polston KFL, Eraslan M, Bickel CS, Windham ST, McLain AB et al. A high-
 641 protein diet or combination exercise training to improve metabolic health in individuals with

- 642 long- standing spinal cord injury: a pilot randomized study. *Physiol Rep*. 2018;6(16).
 643 doi:10.14814/phy2.13813.
- 644 90. Thompson JD, Peacock AO, Betts AJ. Substitution and Compensation Erode the Energy
 645 Deficit from Exercise Interventions. *Med Sci Sports Exerc*. 2014;46(2):423-.
 646 doi:10.1249/MSS.0000000000000164.
- 647 91. Nightingale TE, Williams S, Thompson D, Bilzon JLJ. Energy balance components in
 648 persons with paraplegia: daily variation and appropriate measurement duration. *The*
 649 *international journal of behavioral nutrition and physical activity*. *Int J Behav Nutr Phys Act*.
 650 2017;14(1):132. doi:10.1186/s12966-017-0590-z.
- 651 92. Radziuk J. Homeostatic model assessment and insulin sensitivity/resistance. *Diabetes*.
 652 2014;63(6):1850. doi:10.2337/db14-0116.
- 653 93. Matsuda M, DeFronzo R. Insulin sensitivity indices obtained from oral glucose tolerance
 654 test: Comparison with the euglycemic insulin clamp. *Diabetes*. 1999;48:A79-A.
- 655 94. Gorgey AS, Graham ZA, Bauman WA, Cardozo C, Gater DR. Abundance in proteins
 656 expressed after functional electrical stimulation cycling or arm cycling ergometry training in
 657 persons with chronic spinal cord injury. *J Spinal Cord Med*. 2017;40(4):439-48.
 658 doi:10.1080/10790268.2016.1229397.
- 659 95. Mann S, Beedie C, Jimenez A. Differential Effects of Aerobic Exercise, Resistance
 660 Training and Combined Exercise Modalities on Cholesterol and the Lipid Profile: Review,
 661 Synthesis and Recommendations. *Sports Medicine*. 2014;44(2):211-21. doi:10.1007/s40279-
 662 013-0110-5.
- 663 96. Gilbert O, Croffoot JR, Taylor AJ, Nash M, Schomer K, Groah S. Serum lipid
 664 concentrations among persons with spinal cord injury - A systematic review and meta-
 665 analysis of the literature. *Atherosclerosis*. 2014;232(2):305-12.
 666 doi:10.1016/j.atherosclerosis.2013.11.028.

667 **Figure 1.** PRISMA flow diagram





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Appendix
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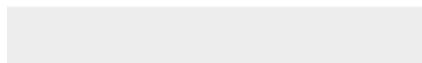


Figure 1

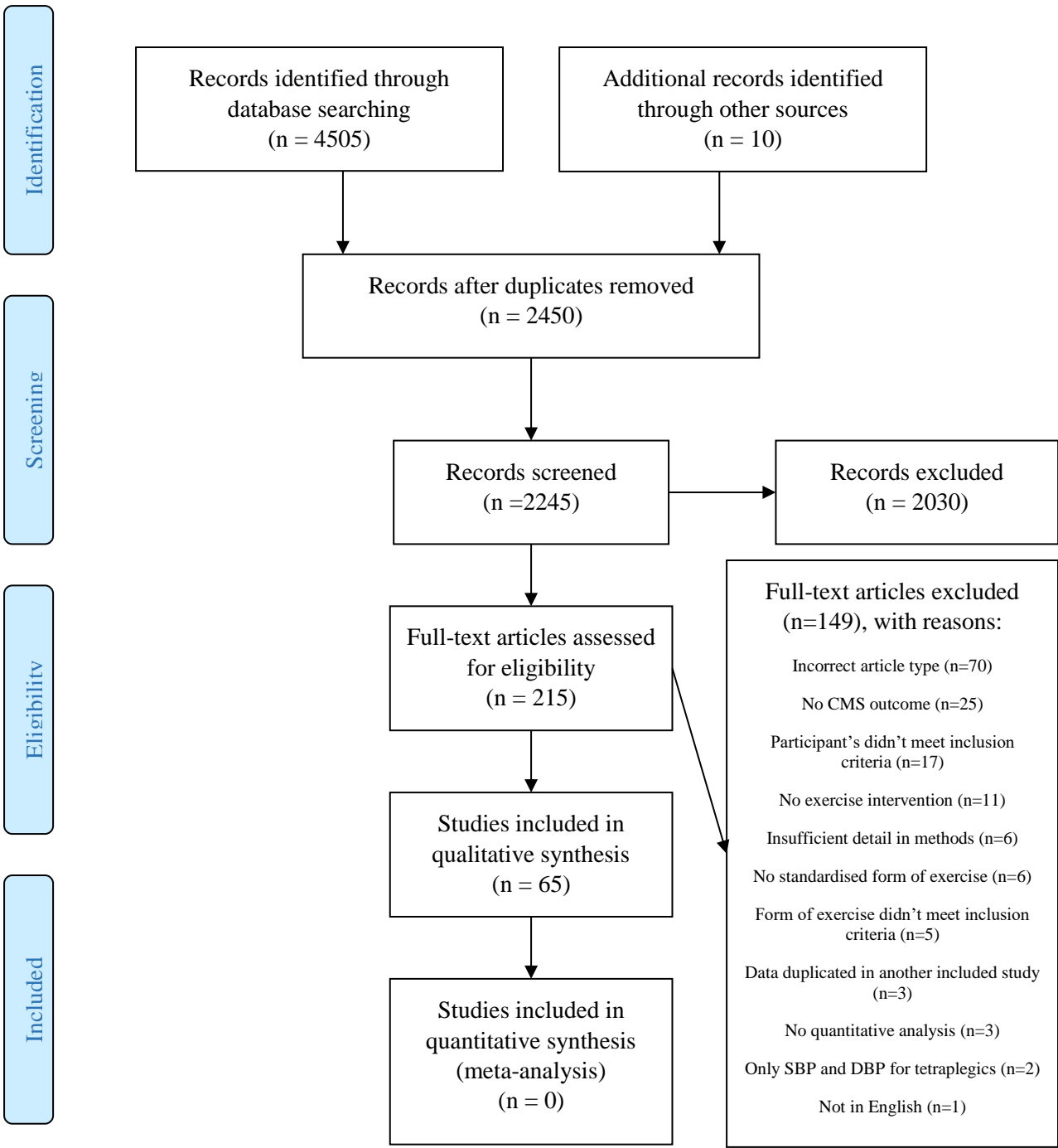


Table 1

Table 1. CMS outcome measures		
Central Adiposity/Obesity	Body Mass Index (BMI)	Formatted: Pattern: Clear (Yellow)
	Body Mass (BM)	
	Waist Circumference (Waist)	
	Hip Circumference	
	Waist to Hip Ratio (WHR)	Formatted: Pattern: Clear (Yellow)
	Body Fat Percentage (BF%) (assessed via DEXA/CT)	
	Fat Mass (FM) (assessed via DEXA/CT)	
	Android Fat Mass	
	Visceral Adipose Tissue (VAT)	
	Liver Fat Content	
	Leptin	
Glycaemic Control	Fasting insulin and glucose	
	Glucose to insulin ratio	
	Fasting proinsulin	
	Glycosylated haemoglobin (HbA1c)	
	Fasting/postprandial insulin sensitivity measures	
	C-peptide	
Dyslipidaemia	Triglycerides (TG)	Formatted: Pattern: Clear (Yellow)
	Low-density lipoprotein-cholesterol (LDL-C)	
	High-density lipoprotein-cholesterol (HDL-C)	
	Total cholesterol (TC)	
	DL, HDL, TC, TC: HDL-C	
	Non-esterified fatty acids (NEFA)	
	Free-fatty acids (FFA)	
	Apolipoprotein B	
Inflammation	C-reactive Protein (CRP)	
	Interleukin-6 (IL-6)	
	Tumour necrosis factor-alpha (TNF-α)	
	Adiponectin	
Vascular Dysregulation	Systolic Blood Pressure (SBP)	Formatted: Pattern: Clear (Yellow)
	Diastolic Blood Pressure (DBP)	
	Pulse wave velocity (PWV)	
	Flow-mediated dilation (FMD)	
	Microalbuminuria	
Thrombotic State	Fibrinogen	
	Plasminogen activator inhibitor-1 (PAI-1)	

Table 2

Table 2. Summary coding of studies examining the effect of exercise on CMS outcome measures.

		Aerobic	Aerobic + RT	Ambulation	Hybrid and Rowing	FES-cycling	FES-RT/Combined
Central Adiposity/Obesity	BM	1/9 (11%)	1/2 (50%)	1/3 (33%)	0/5 (0%)	1/4 (25%)	0/4 (0%)
	BMI	1/4 (25%)	1/4 (25%)	1/1 (100%)	0/1 (0%)	0/2 (0%)	1/3 (33%)*
	Waist	4/6 (66%)	2/3 (67%)	-	1/2 (50%)	-	-
	WHR	-	1/1 (100%)	-	-	-	-
	BF%	0/2 (0%)	-	2/2 (100%)	0/2 (0%)	1/2 (50%)	0/2 (0%)
	FM	0/3 (0%)	1/2 (50%)	0/2 (0%)	-	1/2 (50%)	0/2 (0%)
	Android FM	0/1 (0%)	-	-	0/1 (0%)	-	-
	Abdominal AT	-	-	-	--	0/1 (0%)	-
	VAT	0/1 (0%)	1/1 (100%)	-	--	-	0/2 (0%)
	Leptin	1/1 (100%)	0/1 (0%)	-	1/1 (100%)	-	-
Inflammation	CRP	0/1 (0%)	--	1/1 (100%)	0/1 (0%)	1/2 (50%)	0/1 (0%)
	IL-6	1/2 (50%)	0/1 (0%)	-	0/1 (0%)	1/2 (50%)	0/1 (0%)
	TNF- α	1/1 (100%)	0/1 (0%)	-	-	1/2 (50%)	0/1 (0%)
	Adiponectin	0/1 (0%)	0/1 (0%)	-	-	-	1/1 (100%)
Dyslipidaemia	TG	1/6 (17%)	2/4 (50%)	0/2 (0%)	1/1 (100%)	1/3 (33%)	1/3 (33%)
	FFA	-	-	-	-	0/1 (0%)	0/1 (0%)
	NEFA	0/1 (0%)	-	-	-	-	-
	TC	1/6 (17%)	2/5 (40%)	1/2 (50%)	0/1 (0%)	0/2 (0%)	1/3 (33%)
	HDL-C	0/7 (0%)	1/5 (20%)	0/2 (0%)	0/2 (0%)	1/3 (33%)	1/3 (33%)
	LDL-C	0/5 (0%)	2/5 (40%)	1/2 (50%)	0/1 (0%)	1/3 (33%)	0/3 (0%)
	TC: HDL-C	0/1 (0%)	1/2 (50%)	1/1 (100%)	-	1/1 (100%)	1/2 (50%)
Glycaemic Control	Fasting Glucose	0/8 (0%)	0/3 (0%)	0/1 (0%)	1/2 (50%)	0/1 (0%)	0/2 (0%)
	Fasting Insulin	4/5 (80%)	1/3 (33%)	-	0/2 (0%)	0/3 (0%)	0/1 (0%)
	HbA1c	0/1 (0%)	0/1 (0%)	-	-	-	-
	HOMA-IR	4/4 (100%)	2/2 (100%)	-	0/2 (0%)	-	0/2 (0%)
	HOMA-%S	1/1 (100%)	-	-	-	-	0/1 (0%)
	HOMA-% β	0/2 (0%)	-	-	-	-	0/1 (0%)
	ISI-Matsuda	0/2 (0%)	-	-	-	-	-
	Glucose OGTT	0/2 (0%)	-	1/1 (100%)	0/1 (0%)	2/3 (66%)	0/3 (0%)
	Insulin OGTT	0/2 (0%)	-	1/1 (100%)	-	1/3 (33%)	0/2 (0%)
	IVGTT Si	0/1 (0%)	-	-	-	0/2 (0%)	0/1 (0%)
	Cederholm Index	-	-	-	-	1/1 (100%)	-
	HEC Si	-	-	-	-	1/1 (100%)	-
	HEC Glucose	-	-	-	-	1/1 (100%)	-

Thrombotic State	PAI-1	1/2 (50%)	0/1 (0%)	-	-	-	-
	Fibrinogen	0/1 (0%)	-	-	-	0/1 (0%)	-
Vascular Dysregulation	SBP	1/9 (11%)	0/3 (0%)	0/3 (0%)	0/2 (0%)	1/4 (25%)	0/1 (0%)
	DBP	0/9 (0%)	0/3 (0%)	0/3 (0%)	1/2 (50%)	1/3 (33%)	0/1 (0%)
	FMD	-	0/1 (0%)	-	1/2 (50%)	-	1/1 (100%)
	PWV	-	0/1 (0%)	-	-	0/1 (0%)	-
	Albumin	-	-	-	-	-	0/1 (0%)

Black fill, white text: 0-33% of studies reported significant differences; grey fill, black text: 34-59% of studies reported significance differences; grey fill, white text: 60-100% of studies demonstrated positive significance differences, bold writing: ≥ 4 studies demonstrate the same effect. *one study reported a significant increase in BMI. NA; not applicable

HOMA-IR; *homeostatic model assessment insulin resistance*, HOMA-%S; *insulin sensitivity*; HOMA-% β ; *beta cell function*, ISI-Matsuda; *insulin sensitivity index-Matsuda*. OGTT; *oral glucose tolerance test*, IVGTT Si; *intravenous glucose tolerance test insulin sensitivity*, HEC Si; *hypereuglycaemic clamp insulin sensitivity*.

Table 3. Detailed findings from voluntary upper-body aerobic exercise studies included in this review.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline Intervention (Control) Mean \pm SD	Change Intervention (Control)	p value*	ES
[25] Pre-post† 20 High	10	Hand-cycle 16 weeks 2 sessions/week 65-75% HRR 18-32 mins	Waist (cm) Android Fat Mass (kg) Android Fat (%) TG (mmol/L) HDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR SBP (mmHg) DBP (mmHg) CRP (mg/L) IL-6 (pg/mL)	89.7 \pm 3.5 2.6 \pm 0.4 38.6 \pm 3.7 1.2 \pm 0.2 1.4 \pm 0.2 5.3 \pm 0.2 54.6 \pm 8.5 1.9 \pm 0.3 119 \pm 4 72 \pm 3 2.86 \pm 1.36 2.40 \pm 0.57	-2.5 0.0 -1.3 -0.1 0.0 -0.2 -14.3 -0.5 +4 -3 -0.39 -0.64	0.03 0.85 0.26 0.67 0.94 0.30 0.01 0.02 0.30 0.34 0.23 0.10	0.75 0.00 0.40 0.63 0.00 1.00 1.78 2.35 1.13 0.57 0.28 0.56
[26] RCT 19 High	21	ACE 6 weeks 4 sessions/week 60-65% $\dot{V}O_{2PEAK}$ 45 mins	Body Mass (kg) Fat Mass (kg) VAT (cm ²) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) NEFA (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA2-IR HOMA2-%B (%) ISI-Matsuda Glucose OGTT (%) Insulin OGTT (%) SBP (mmHg) DBP (mmHg)	76.8 \pm 13.3 (76.8 \pm 11.3) 27.6 \pm 10.0 (25.5 \pm 6.6) 181 \pm 85 (186 \pm 47) 1.2 \pm 0.5 (1.3 \pm 0.5) 4.9 \pm 1.0 (5.1 \pm 0.9) 1.1 \pm 0.3 (1.0 \pm 0.2) 3.2 \pm 0.9 (3.5 \pm 0.8) 0.6 \pm 0.3 (0.7 \pm 0.6) 5.3 \pm 0.5 (5.7 \pm 1.3) 54.8 \pm 30.1 (41.3 \pm 18.1) 1.03 \pm 0.57 (0.80 \pm 0.35) 87 \pm 31 (66 \pm 23) 4.8 \pm 2.2 (6.4 \pm 3.1) - - 128 \pm 23 (128 \pm 15) 77 \pm 15 (81 \pm 13)	-1.1 (-0.7) -0.6 (0.0) -22 (-3) -0.1 (+0.5) -0.1 (+0.1) +0.1 (0.0) 0.0 (-0.2) +0.3 (-0.1) 0.0 (0.0) -12.7 (+3.1) -0.24 (+0.06) -14 (+1) +0.3 (-0.7) +8 (-9) -8 (+6) -3 (-2) -1 (-4)	NS NS NS NS NS NS NS NS NS 0.03 0.04 NS NS NS NS NS	- - - 1.02 0.17 0.07 0.05 0.40 - 0.54 0.49 0.58 - - - - -
[27] RCT 19 High	17	ACE 12 weeks 3 sessions/week 50-65% HRR 20-30 mins	BMI (kg/m²) Waist (cm) Leptin (ng/mL) PAI-1 (ng/mL) IL-6 (pg/mL) TNF-α (pg/mL) Adiponectin (ng/mL)	27.6 \pm 4.1 (27.8 \pm 4.4) 98.1 \pm 6.6 (98.4 \pm 6.7) 9.6 \pm 2.7 (9.8 \pm 2.8) 29.8 \pm 6.2 (30.2 \pm 6.1) 6.7 \pm 2.2 (6.9 \pm 2.3) 23.3 \pm 5.6 (23.6 \pm 5.5) 18.8 \pm 4.1 (18.5 \pm 4.2)	-0.2 (NR) -3.7 (NR) -2.1 (+0.1) -0.7 (-0.1) -2.6 (+0.1) -2.7 (-0.1) +0.6 (+0.1)	0.72 0.05 <0.05 NS <0.05 <0.05 NS	- - 0.71 0.09 1.08 0.47 0.11
[28] Pre-post 17 Fair	10	ACE 10 weeks 3 sessions/week 70% $\dot{V}O_{2PEAK}$ 30 mins	BF (%) Fat Mass (kg) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) Glucose: Insulin Glucose OGTT (AUC) Insulin OGTT (AUC) HOMA-IR HOMA-%B (%) HOMA %S (%) ISI-Matsuda	34.9 \pm 34.9 25.1 \pm 11.9 4.50 \pm 0.58 0.94 \pm 0.16 2.71 \pm 0.39 5.54 \pm 0.82 84.9 \pm 38.8 9.77 \pm 4.49 - - 1.6 \pm 0.7 111.4 \pm 48.7 73.3 \pm 31.6 3.4 \pm 1.6	0.0 -0.3 +0.04 -0.06 +0.31 -0.05 -31.8 +3.92 +6% +5% -0.6 -29.0 +32.3 +0.2	0.35 0.75 0.75 0.07 0.12 0.92 0.03 0.03 0.25 0.92 0.05 0.12 0.05 0.35	0.01 0.02 0.08 0.22 0.72 0.06 1.07 1.00 0.29 0.13 1.11 0.78 1.10 0.16
[29] Pre-post 17 Fair	5	ACE 12 weeks 3 sessions/week Anaerobic Threshold 30 mins	Body Mass (kg) BMI (kg/m²) SBP (mmHg) DBP (mmHg)	65.6 \pm 6.6 23.5 \pm 3.4 110 \pm 25 66 \pm 12	+2.3 +0.8 +1 +2	0.18 0.18 0.13 0.80	0.33 0.22 0.04 0.11
[30] Pre-post 17 Fair	14	ACE 10 weeks 3 sessions/week 25-35 mins	Body Mass (kg)	69.2	-2	NS	-

		60% W _{PEAK}					
[31] Pre-post† 16 Fair	4	ACE 16 weeks 5 sessions/week 75% HR _{MAX} 40 mins	Body Mass (kg) BMI (kg/m²) BF (%) Fat Mass (kg) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) IVGTT Insulin Sensitivity IVGTT Glucose Effectiveness SBP (mmHg) DBP (mmHg)	80 ± 12 28 ± 4 40 ± 3.7 31 ± 7 5.27 ± 0.50 76.4 ± 62.5 - - 119 ± 13 75 ± 5	0 0 -2 -2 -0.06 -23.6 +62.5% +35% -1 +2	NS NS NS NS 0.9 NS NS NS NS	0.00 0.00 0.52 0.31 0.08 0.41 0.64 0.70 0.08 0.36
[32] RCT 16 Fair	33	ACE 12 weeks 3 sessions/week 50-70% V̇O _{2PEAK} 30 mins	Waist (cm) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) SBP (mmHg) DBP (mmHg)	86.5 (94.5) 1.50 (1.38) 4.57 (4.60) 0.96 (1.05) 2.87 (2.91) 4.44 (4.47) 100 (100) 60 (60)	+4.75 (+1.5) +0.06 (+0.29) +0.26 (+0.05) 0.0 (+0.14) 0.0 (0.09) -0.19 (+0.14) 0 (0) 0 (0)	NS NS NS NS NS NS NS NS	- - - - - - - -
[33] RCT 15 Fair	16	Hand-cycle 6 weeks 3 sessions/week 70-80% HR _{PEAK} 44 mins	BMI (kg/m²) Waist (cm) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR	22.0 ± 3.7 (20.8 ± 2.7) 88.3 ± 13.1 (81.7 ± 9.0) 1.16 ± 0.47 (1.09 ± 0.56) 4.56 ± 0.92 (4.73 ± 0.55) 1.10 ± 0.30 (1.17 ± 0.18) 2.93 ± 0.67 (3.07 ± 0.62) 4.36 ± 0.46 (4.92 ± 0.60) 37.5 ± 16.7 (34.0 ± 20.1) 1.0 ± 0.6 (1.1 ± 0.8)	-0.2 (+0.3) -2.6 (+0.8) -0.01 (-0.12) +0.03 (-0.09) +0.09 (-0.01) -0.06 (-0.03) -0.09 (+0.04) -13.9 (+11.8) -0.4 (0.4)	<0.01 <0.01 0.95 0.81 0.29 0.99 0.32 <0.01 <0.01	1.58 2.67 0.25 0.25 0.82 0.09 0.39 1.57 1.40
[34] Pre-post 14 Fair	9	ACE 10 weeks 4 sessions/week 50-70% HRR 60 mins	Body Mass (kg) Waist (cm) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) HbA1c (%) PAI-1 (g/L) Fibrinogen (g/L) SBP (mmHg) DBP (mmHg)	61.0 ± 7.0 85.5 ± 6.2 1.74 ± 0.78 5.25 ± 0.88 1.45 ± 0.18 2.95 ± 0.62 5.66 ± 1.39 4.9 ± 0.6 5.2 ± 1.1 2.97 ± 5.7 136 ± 5 75 ± 8	-1.9 -1.9 -0.43 -0.18 +0.05 -0.10 -0.17 -0.10 -1.4 -0.7 -3 -2	<0.05 <0.05 <0.05 NS NS NS NS NS <0.05 NS <0.05 NS	0.26 0.26 0.31 0.14 0.20 0.15 0.10 0.14 1.22 0.14 0.66 0.30
[35] Pre-post 14 Fair	12	WCE 10 weeks 2-3 sessions/week Intensity NR 20-30 mins	Body Mass (kg) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) TC: HDL-C Fasting Glucose (mmol/L) SBP (mmHg) DBP (mmHg)	74 ± 10 1.32 ± 0.59 4.78 ± 1.09 1.24 ± 0.26 4 ± 1 4.77 ± 1.94 124 ± 10 85 ± 7	+2.0 -0.08 -0.39 0.0 -0.2 -1.0 0 -3	NS NS 0.04 NS NS NS NS NS	0.20 0.12 0.40 0.00 0.20 0.03 0.00 0.35
[36] Pre-post 14 Fair	12	WCT 12 weeks 14 sessions/week 60-70% HR _{PEAK}	Body Mass (kg)	41.8 ± 5.8	0.0	NS	0.00
[37] Pre-post 13 Low	9	WCT 7 weeks 5 sessions/week Intensity NR Duration NR	Body Mass (kg) Waist (cm)	82.1 ± 14.6 109.6 ± 12.2	+1.2 +4.1	NS NS	0.09 0.28
[38] Pre-post 12 Low	11	WCE 5 weeks 2 sessions/week <80% HR _{PEAK} 30 mins	SBP (mmHg) DBP (mmHg)	126 ± 12 82 ± 6	-2 -2	NS NS	0.16 0.29
[39] Non-randomised	14	ACE 16 weeks 3 sessions/week	SBP (mmHg) DBP (mmHg)	122 ± 5 (114 ± 6) 78 ± 5 (81 ± 4)	+4 (+18) -2 (+6)	NS NS	- -

controlled trial 11 Low		50 or 70% $\dot{V}O_{2PEAK}$ 20 or 40 mins					
[40] Pre-post 11 Low	11	WCE 8 weeks 3 sessions/week 70-80% HRR (or 50-60% HRR) 20 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C	1.08 ± 0.32 (0.88 ± 0.26) 5.04 ± 0.91 (4.81 ± 0.70) 1.01 ± 0.28 (1.27 ± 0.28) 3.54 ± 0.67 (3.15 ± 0.44) 5 ± 0.9 (4 ± 0.7)	-0.20 (-0.04) -0.41 (+0.16) +0.21 (-0.18) -0.54 (0.16) -1 (+1)	<0.1 (NS) NS (NS) <0.1 (NS) <0.1 (NS) <0.1 (NS)	0.76 (0.15) 0.63 (0.28) 0.83 (0.46) 1.12 (0.37) 1.37 (0.67)

Red font clinically high group average, bold font significant difference following intervention reported, ES effect size.

ACE *arm-crank ergometry*, WCE *wheelchair ergometer*, WCT *wheelchair treadmill ergometry*, HRR *heart rate reserve*, $\dot{V}O_{2PEAK}$ *peak oxygen uptake*, W_{PEAK} *peak power output*, HR_{PEAK} *peak heart rate*, HR_{MAX} *age-predicted maximum heart rate*, BF *body fat*, HOMA-IR *homeostatic model assessment of insulin resistance*, OGTT *oral glucose tolerance test*, AUC *area under the curve*, IVGTT *intravenous glucose tolerance test*, NS *non-significant*, NR *not reported*

*Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs.

† True study design is RCT, presented as pre-post due to two different exercise modalities being tested.

Table 4. Detailed findings from upper-body RT (with or without aerobic training) studies included in this review.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline <i>Intervention (Control)</i> Mean \pm SD	Change <i>Intervention (Control)</i>	p value *	ES
[41] Pre-post† 23 High	17	16 weeks 3 sessions/week RT: 20-25 mins, 2-3 sets at 12-15 repetition max resistance Aerobic: 20-25 mins, 3-5 RPE	Fat Mass (kg)	23.2 \pm 10.8	-0.2	NS	0.02
[42] RCT 19 High	23	16 weeks 2 sessions/week RT: 3 x 10, 50-70% 1RM Aerobic: >20 mins, 3-6 RPE	Body Mass (kg) BMI (kg/m²) Waist (cm) Fat Mass (kg) VAT (kg) Leptin (ng/mL) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C Fasting Insulin (pmol/L) HbA1c (mmol/L) PAI-1 (ng/mL) SBP (mmHg) DBP (mmHg) Brachial FMD Femoral FMD PWV – Central IL-6 (pg/mL) TNF- α (pg/mL) Adiponectin (μ g/mL)	83.4 \pm 18.9 (78.6 \pm 15.7) 27.3 \pm 5.2 (25.7 \pm 4.9) 96.2 \pm 14.9 (89.6 \pm 11.7) - (-) - (-) 10.12 \pm 13.25 (10.2 \pm 12.8) 1.3 \pm 0.6 (1.1 \pm 0.7) 4.5 \pm 0.9 (4.1 \pm 0.9) 1.01 \pm 0.2 (1.13 \pm 0.2) 2.9 \pm 0.9 (2.5 \pm 0.7) 4.6 \pm 0.9 (3.8 \pm 1.1) 39.2 \pm 29.5 (68.2 \pm 77.9) 1.01 \pm 0.2 (1.13 \pm 0.3) 30.4 \pm 17.7 (31.1 \pm 22.7) 116 \pm 18 (118 \pm 18) 68 \pm 9 (74 \pm 13) - - - 2.5 \pm 2.2 (3.7 \pm 2.1) 4.7 \pm 1.8 (4.1 \pm 2.2) 76.7 \pm 64.0 (82.02 \pm 38.28)	↓ -0.3 (+0.9) -1.0 (+3.5) ↓ ↓ +1.0 (+4.1) +0.1 (-0.1) -0.2 (0.0) 0.0 (+0.04) -0.2 (-0.1) -0.2 (-0.2) +9.5 (+10.3) +0.9 (-0.2) +11.6 (+15.5) 0 (-2) -1 (-2) - - - -1.0 (+1.8) -0.3 (-0.1) +13.4 (+35.67)	0.03 0.02 0.03 0.04 0.04 NS NS NS NS NS NS NS NS NS 0.31 0.66 0.526 NS NS NS	1.07 1.14 1.02 1.00 1.02 - - - - - - - - - - - - - - - - -
[43] RCT 17 Fair	20	8 weeks 3 sessions/week RT: 60-80% 1RM, 5 exercises.	BMI (kg/m²) Waist: Hip TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR	25.3 \pm 1.4 (24.9 \pm 1.0) 0.83 \pm 0.02 (0.83 \pm 0.14) 1.77 \pm 0.07 (1.80 \pm 0.11) 4.66 \pm 0.18 (4.78 \pm 0.10) 1.12 \pm 0.06 (1.15 \pm 0.11) 2.81 \pm 0.10 (2.82 \pm 0.12) 5.46 \pm 1.34 (5.45 \pm 1.42) 110.6 \pm 19.5 (116.7 \pm 24.9) 6.92 \pm 1.27 (7.27 \pm 2.09)	-0.6 (+0.2) -0.02 (+0.01) -0.27 (+0.02) -0.38 (+0.04) +0.12 (+0.01) -0.12 (+0.05) -0.38 (-0.01) -2.4 (-3.5) -0.62 (-0.25)	NS 0.03 0.001 0.001 NS 0.001 NS NS 0.03	- - - - - - - - -
[44] RCT 17 Fair	17	6 weeks 3 sessions/week RT: 1-3 x 10-20 mins, 4-8 RPE or 65-85% HR _{MAX}	BMI (kg/m ²) Waist (cm) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR	21.8 \pm 2.9 (20.8 \pm 1.9) 84.1 \pm 11.9 (79.4 \pm 6.6) 4.20 \pm 0.88 (1.96 \pm 0.09) 1.26 \pm 0.55 (1.32 \pm 0.27) 2.42 \pm 0.81 (3.25 \pm 0.76) 4.50 \pm 0.30 (4.20 \pm 0.20) 52.1 \pm 32.6 (20.1 \pm 7.6) 1.5 \pm 1.0 (0.5 \pm 0.2)	-0.4 (-0.1) -2.6 (-0.2) -0.04 (+0.05) +0.14 (-0.04) -0.12 (+0.36) -0.09 (+0.10) -20.1 (+2.1) -0.6 (+0.06)	0.08 0.02 0.46 0.05 0.12 0.23 0.05 0.05	1.17 1.94 0.40 1.24 0.85 0.62 1.24 1.33
[45] Pre-post 15 Fair	16	12 weeks 3 sessions/week RT: 2 x 8 to 3 x 12. Aerobic: 60-75% HRR 20-60 mins	Body Mass (kg) BMI (kg/m²) Waist (cm) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) SBP (mmHg) DBP (mmHg)	74.9 \pm 7.2 26.0 \pm 2.6 104.1 \pm 7.9 1.41 \pm 0.93 5.66 \pm 1.32 1.26 \pm 0.40 4.20 \pm 1.15 5.81 \pm 0.05 118 \pm 20 80 \pm 11	-2.9 -1.0 +1.3 -0.30 -0.68 +0.02 -0.19 -0.74 -5 -3	NS NS NS <0.05 <0.05 NS NS NS NS NS	1.19 0.33 0.17 0.35 0.54 0.05 0.17 1.64 0.26 0.27
[46] RCT	34	36 weeks 2 sessions/week	SBP (mmHg)* DBP (mmHg)*	125 \pm 23 (133 \pm 20) 72 \pm 16 (85 \pm 14)	+2 (-2) +3 (-4)	NS NS	- -

15 Fair		RT: 70-80% 1RM, Aerobic: 15-30 mins, 70% HR _{MAX} or 3-4 RPE.	*Paraplegics only				
[47] Pre-post 12 Low	5	12 weeks 3 sessions/week Circuit Training: 50-60% 1RM 40-45 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C	2.29 ± 1.35 4.73 ± 0.67 1.05 ± 0.14 3.06 ± 0.57 5.0 ± 1.1	-0.14 -0.42 +0.11 -0.79 -1.1	0.63 0.20 0.10 0.05 0.05	0.12 0.56 0.49 1.17 1.19

1RM *one-rep maximum*, RPE *rating of perceived exertion*. *Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs. †True study design is RCT, presented as pre-post due to two different exercise modalities being tested

Table 5. Detailed findings of FES-cycling studies included in this review.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline <i>Intervention (Control)</i> Mean \pm SD	Change <i>Intervention (Control)</i>	p value *	ES
[48] Pre-post 16 Fair	1 0	FES-cycling 12 weeks 3 sessions/week 90-95% of max tolerance 1-45 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) CRP (pg/mL) IL-6 (pg/mL) TNF- α (pg/mL)	0.37 \pm 0.19 1.99 \pm 0.46 0.48 \pm 0.13 1.13 \pm 0.33 12.59 \pm 14.06 6.29 \pm 4.65 25.62 \pm 49.64	-0.01 +0.07 0.0 +0.07 -5.81 +0.61 +4.27	NS NS NS NS NS NS NS	0.06 0.15 0.00 0.22 0.55 0.13 0.07
[49] Retrospective cohort study 16 Fair	4 5	FES-cycling 3-168 weeks 3 sessions/week Intensity NR 45-60 mins	TG HDL-C LDL-C TC: HDL-C	NR NR NR 4.1 \pm 1.0 (5.3 \pm 1.9)	- - - -	<0.05 NS <0.05 0.03	- - - 0.79
[31]† Pre-post 16 Fair	9	FES-cycling 16 weeks 5 sessions/week 75% HR _{MAX} 40 mins	Body Mass (kg) BMI (kg/m²) BF (%) Fat Mass (kg) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) IVGTT Insulin Sensitivity (%) IVGTT Glucose Effectiveness (%) SBP (mmHg) DBP (mmHg)	79 \pm 12 26 \pm 5 38 \pm 5.7 29 \pm 8.6 5.00 \pm 0.11 97.2 \pm 118.1 - - 123 \pm 8 79 \pm 5	+6 +3 0 0 +0.33 -59.0 +129 +4 +4 +4	NS NS NS NS 0.4 0.8 NS NS >0.5 >0.5	0.59 0.82 0.00 0.00 0.65 0.70 0.69 0.19 0.44 0.36
[50] Pre-post 14 Fair	7	FES-cycling 8 weeks 3 sessions/week Max load to finish 30 min 30 min	2-h Glucose OGTT (mmol/L) 2-h Insulin OGTT (pmol/L)	7.77 \pm 0.89 822 \pm 296	-0.98 -215	0.01 NS	2.13 1.00
[51] Pre-post 14 Fair	9	FES-cycling 6 weeks 3 sessions/week Max load to finish 30 min 30 min	SBP (mmHg)	131 \pm 20	+6	NS	0.40
[52] Pre-post 14 Fair	1 8	FES-cycling 8 weeks 3 sessions/week Intensity NR 30 mins	Body Mass (kg) BMI (kg/m²)	73.8 \pm 13.9 25.4 \pm 3.9	+1.2 +0.3	0.06 NS	0.09 0.08
[53] Pre-post 13 Low	1 3	FES-cycling 12 weeks 3 sessions/week Max load to finish 30 min 30 min	SBP (mmHg) DBP (mmHg) *paraplegics only	- - 	↓ ↓ 	<0.05 <0.05 	- -
[54] Pre-post 13 Low	1 8	FES-cycling 10 weeks 2-3 sessions/week Max load to finish 30 min or fatigue	Body Mass (kg) Fat Mass (kg) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) 2-h Glucose OGTT 2-h Insulin OGTT CRP IL-6 TNF-α	69.6 \pm 4.2 22.9 \pm 2.3 1.18 \pm 0.30 4.08 \pm 0.16 0.88 \pm 0.05 2.65 \pm 0.16 - - 15.92 \pm 1.57 4.91 \pm 1.10 11.82 \pm 0.63	-2.1 +0.6 -0.04 -0.04 -0.10 +0.07 ↓ ↓ -2.98 -1.12 -0.51	<0.05 <0.05 NS NS <0.05 NS <0.05 <0.05 <0.05 <0.05 <0.05	0.12 0.06 0.04 0.06 0.43 0.12 - - 0.57 0.31 0.19
[55] Pre-post 13 Low	8	FES-cycling 6 weeks 3 sessions/week Intensity NR 30 mins	SBP (mmHg) DBP (mmHg)	112 \pm 6 77 \pm 4	-3 -4	NS NS	0.63 1.00

[56] Pre-post 12 Low	5	FES-cycling 8 weeks 7 sessions/week Max load to finish 30 min 30 mins	BF (%) Fasting Insulin	29.7 ± 2.6 NR	-1.9 NR	<0.05 NS	0.80 -
[57] Pre-post 12 Low	1 2	FES-cycling 4 weeks 2 sessions/week Intensity NR 30 mins	Fibrinogen (mg/dL)	410 ± 78	+29	NS	0.17
[58] Pre-post 11 Low	5	FES-cycling 8 weeks 7 sessions/week Max load to finish 30 min 30 mins	HEC Glucose Uptake (%)	-	+33	<0.05	0.95
[59] Pre-post 11 Low	8	FES-cycling 8 weeks 2-3 sessions/week Max load to finish 30 min 30 mins	Hyperaemic Flow	-	↔	NS	-
[60] Pre-post 11 Low	1 0	FES-cycling 52 weeks 3 sessions/week Intensity NR 30 mins	FFA (mmol/L) Fasting Insulin (pmol/L) Glucose OGTT (AUC) Insulin OGTT (AUC) HEC SSGIR Step 1 (%) HEC SSGIR Step 2 (%)	0.68 ± 0.08 83 ± 35 - - - -	-0.03 -28 ↔ ↔ +28 +17	NS NS NS NS <0.05 NS	0.13 0.33 - - 0.74 0.63
[61] Pre-post 10 Low	1 5	FES-cycling 26 weeks 3 sessions/week Max load to finish 30 min 30 mins	Body Mass Abdominal Adipose Tissue	NR NR	↔ ↔	NS NS	- -
[62] Pre-post 9 Low	5	FES-cycling 8 weeks 3 sessions/week Intensity NR 30 mins	Cederholm Index	-	↑	<0.05	-

*Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs.

†True study design is RCT, presented as pre-post due to two different interventions (vs. high-protein diet).

Table 6. Detailed findings of FES-RT and combined (FES-cycling and FES-RT) studies included in this review.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline Intervention (Control) Mean \pm SD	Change Intervention (Control)	p value *	ES
[63] RCT 21 High	22	FES-knee extensions (with testosterone replacement therapy) 16 weeks 2 sessions/week 4 x 10 ~1 kg increments every 2 sessions	Body Mass (kg) BMI (kg/m²) BF (%) Fat Mass (kg) VAT (cm ²) TG FFA TC HDL-C LDL-C IVGTT Insulin Sensitivity (%) IVGTT Glucose Effectiveness (%) CRP IL-6 (pg/mL) TNF- α Adiponectin (ng/mL)	80.5 \pm 16 (77.5 \pm 9.0) 25 \pm 4.5 (24.4 \pm 3.6) 32 \pm 11 (33.4 \pm 9) 26.7 \pm 12.5 (26.1 \pm 8.0) 101 \pm 71 (91.5 \pm 49.5) NR NR NR NR NR - - NR 5.5 \pm 5.6 (5.9 \pm 6.0) NR 4323 \pm 1856 (3516 \pm 1205)	+2.6 (+0.2) +1.6 (-0.4) -1.3 (-1.4) 0.0 (-1.0) -13 (-7.0) \leftrightarrow \leftrightarrow \leftrightarrow \leftrightarrow \leftrightarrow 0.0 (0.0) 31.5 (28.6) \leftrightarrow -2.6 (-2.0) \leftrightarrow -624 (+1291)	NS 0.004 NS NS NS NS NS NS NS NS NS NS NS NS <0.05	- - - - - - - - - - - - - -
[64] RCT 16 Fair	9	FES knee-extensions 12 weeks 2 sessions/week 4 x 10 Increased by ~1kg every 2 sessions	Body Mass (kg) BMI (kg/m²) BF (%) Fat Mass (kg) Trunk VAT CSA (cm ²) TG (mmol/L) FFA (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C HOMA-IR (Log ₁₀) Glucose OGTT (AUC) (%) Insulin OGTT (AUC) (%)	74 \pm 14 (76 \pm 8) 21 \pm 5 (23 \pm 3) 30 \pm 8 (29 \pm 3) 23.3 \pm 9 (22 \pm 2) 103 \pm 80 (106 \pm 32) 1.58 \pm 1.38 (1.25 \pm 0.28) 0.58 \pm 0.1 (0.53 \pm 0.1) 4.19 \pm 1.27 (3.93 \pm 0.70) 0.78 \pm 0.08 (0.83 \pm 0.16) 2.72 \pm 0.93 (2.53 \pm 0.67) 5.6 \pm 2 (5 \pm 1) 0.44 \pm 0.27 (0.33 \pm 0.17) - -	+1 (-1) 0 (0) -1 (-1) -0.7 (1) -9 (-14) -0.60 (+0.16) -0.14 (-0.11) +0.05 (+0.2) +0.08 (-0.03) +0.21 (+0.16) -0.8 (+0.2) -0.03 (+0.06) -6.5 (-8.5) -33.9 (+22.0)	NS NS NS NS NS 0.05 0.3 0.1 0.07 0.5 0.02 NS NS NS	- - - - - - - - - - - - - -
[65] Pre-post 14 Fair	12	FES knee-extensions 12 weeks 3 sessions/week 2 x 30 (25% Max), 1 x 60 (12.5% Max) Increased by 0.5 kg per session	Body Mass (kg)	67.6	-0.7	NS	-
[66] Pre-post 14 Fair	14	FES knee-extensions 16 weeks 2 sessions/week 4 x 10 Increased by 0.9 kg every 2 successful sessions	BMI (kg/m²) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL-C Fasting Glucose (mmol/L) 2-h Glucose OGTT (mmol/L) HOMA-IR HOMA%S HOMA% β	26.7 \pm 4.7 1.55 \pm 0.94 4.76 \pm 1.03 1.09 \pm 0.40 2.95 \pm 0.94 4.8 \pm 1.8 4.94 \pm 1.05 6.62 \pm 4.30 1.6 \pm 1.4 136.0 \pm 112.0 125.0 \pm 68.0	-0.3 -0.13 -0.18 +0.09 -0.21 -0.6 +0.22 +0.85 -0.1 +7.0 -14.0	0.70 0.36 0.05 0.02 0.11 0.43 0.16 0.41 0.73 0.65 0.17	0.07 0.16 0.16 0.24 0.21 0.33 0.07 0.19 0.06 0.07 0.19
[67] Pre-post 14 Fair	5	FES knee extensions 18 weeks 2 sessions/week 4 x 10 Increased by 0.9-1.8 kg every 2 sessions	Posterior Tibial FMD (when adjusted for resting diameter)	-	+3.9%	0.03	-
[68] Pre-post 13 Low	19	Combined 10-32 weeks 3 sessions/week	Albumin	NR	\leftrightarrow	NS	-

		Max load to fatigue or 45 reps (FES knee- extensions) 30 mins (FES-cycling)					
[69] Pre-post 12 Low	11	Combined 13-28 weeks 3 sessions/week Max load to fatigue or 45 reps (FES knee- extensions) Duration NR	SBP (mmHg) DBP (mmHg)	114 ± 4 71 ± 3	-16 -4	NS NS	1.21 0.40
[70] Pre-post 11 Low	5	FES knee-extensions 12 weeks 2 sessions/week 4 x 10 Increased by 0.9-1.8 kg every 2 sessions	Fasting Glucose (mmol/L) Fasting Insulin (mmol/L) 2-h Glucose OGTT (mmol/L) 2-h Insulin OGTT	4.87 ± 0.58 NR 5.98 ± 1.44 NR	0.0 ↔ -0.47 ↔	NS NS NS NS	0.00 - 0.24 -
[71] Pre-post 9 Low	4	Combined 4-12 weeks 5 sessions/week Intensity NR 15 mins each	Body Mass (kg)	67.9 ± 5.2	+4.9	NS	0.65

Table 7. Hybrid and FES-rowing studies included in this review.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline Intervention (Control) Mean \pm SD	Change Intervention (Control)	p value	ES
[25] 20 Pre-post† High	9	Hybrid 16 weeks 2 sessions/week 65-75% HRR 18-32 mins	Waist (cm) Android Fat Mass (kg) Android Fat (%) TG (mmol/L) HDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR SBP (mmHg) DBP (mmHg) CRP (mg/L) IL-6 (pg/mL)	91.8 \pm 4.7 2.0 \pm 0.4 33.4 \pm 2.9 1.7 \pm 0.2 1.1 \pm 0.1 5.7 \pm 0.3 72.7 \pm 10.6 2.8 \pm 0.5 112 \pm 6 69 \pm 3 3.91 \pm 1.75 2.51 \pm 0.91	-3.9 -0.1 -2.1 -0.3 +0.1 +0.1 -18.9 -0.6 +5 -6 -0.71 -0.63	0.02 0.34 0.02 0.01 0.22 0.38 0.11 0.16 0.39 0.04 0.08 0.20	0.92 0.25 0.76 1.50 1.00 0.28 1.66 1.09 0.65 1.70 0.41 0.83
[72] Pre-post 16 Fair	9	Hybrid 6 weeks 2 sessions/week Intensity NR 30 mins	Body Mass (kg) Relative Brachial FMD (%) Relative Femoral FMD (%)	74 \pm 18 - -	+1 - -	0.52 0.28 0.002	0.06 - -
[73] Pre-post 15 Fair	12	FES-rowing 6 weeks 5 sessions/week >70% HR _{MAX} 42.5 mins	BMI (kg/m²) Waist (cm)	23.4 \pm 3.7 84.1 \pm 10.3	-0.4 -2.1	0.06 0.06	0.11 0.21
[74] Pre-post 14 Fair	12	FES-rowing 26 weeks 1.8 \pm 2 sessions/week 75-85% HR _{PEAK} 30 mins	Body Mass (kg)	72.5 \pm 3.9	+0.8	NS	0.20
[75] Pre-post 14 Fair	10	Hybrid 4 weeks 2-3 sessions/week Intensity NR 30 mins	Body Mass (kg) SBP (mmHg) DBP (mmHg) Absolute Brachial FMD (mm) Relative Brachial FMD (%) Absolute Femoral FMD (mm) Relative Femoral FMD (%)	73 \pm 10 123 \pm 18 73 \pm 14	0 -4 -5	0.77 0.17 0.23 0.48 0.68 0.06 0.10	0.00 0.23 0.38 - - - -
[76] Pre-post 14 Fair	10	FES-rowing 6 weeks 3 sessions/week 86 \pm 8% HR _{PEAK} 30 mins	Body Mass (kg) BF (%)	85.1 \pm 19.6 36.9 \pm 5.9	0.0 -0.2	0.18 0.64	0.00 0.03
[77] Pre-post 14 Fair	7	FES-rowing 12 weeks 3-4 sessions/week 80% $\dot{V}O_{2PEAK}$ 200 kcal/session	Body Mass (kg) BF (%) Leptin (ng/mL) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) HOMA-IR	72.1 \pm 3.6 25.5 \pm 1.8 6.9 \pm 1.7 5.73 \pm 0.09 95.1 \pm 14.6 3.6 \pm 0.8	-1.1 -1.1 -2.2 -0.12 -16.7 -0.8	NS 0.07 0.05 <0.05 NS NS	0.14 0.26 0.60 0.73 0.49 0.65
[78] Pre-post 7 Low	8	Hybrid 6 weeks 2 or 3 sessions/week 80-90% HR _{MAX}	TC HDL-C LDL-C Glucose OGTT	NR NR NR NR	NR NR NR NR	NS NS NS NS	- - - -

HR_{PEAK} peak heart rate, HR_{MAX} age-predicted maximum heart rate, HOMA-IR homeostatic model assessment of insulin resistance, OGTT oral glucose tolerance test, NS non-significant, NR not reported

†True study design is RCT, presented as pre-post due to two different exercise modalities being tested.

Table 8. Ambulation studies included in this review.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline Intervention (Control) Mean \pm SD	Change Intervention (Control)	p value*	ES
[41] Pre- post† 23 High	17	FES-walking 16 weeks 3 sessions/week Max load without knee buckling 45 mins	Fat Mass (kg)	25.4	-1.1	NS	0.12
[79] RCT 19 High	18	Robotic BWSTT 12 weeks 3 sessions/week 80-85% HRR 20-45 mins	Body Mass (kg) BF (%)	80.8 \pm 14.6 (94.3 \pm 25.0) 33.6 \pm 7.9 (34.2 \pm 6.9)	-1.0 (-2) -1.2 (-0.9)	0.72 0.20	- -
[80] Pre-post 19 High	10	BWSTT 16 weeks 3 sessions/week Max speed without loss of gait 60 mins	SBP (mmHg) DBP (mmHg)	114 \pm 19 66 \pm 11	-1 -2	0.90 0.62	0.05 0.19
[81] Pre-post 18 Fair	8	BWSTT 26 weeks 3 sessions/week Max load and speed without knee bucking or loss of gait 60 mins	SBP (mmHg) DBP (mmHg)	117 \pm 20 73 \pm 11	-2 -1	NS NS	0.12 0.15
[82] Pre-post 17 Fair	14	BWSTT 6 weeks 5 sessions/week Intensity NR 45 mins	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) CRP (NR) SBP (mmHg) DBP (mmHg)	1.36 \pm 0.17 4.67 \pm 0.54 1.46 \pm 0.31 2.61 \pm 0.37 5.12 \pm 0.67 NR 127 \pm 10 75 \pm 5	-0.20 -0.14 +0.07 -2.9 -0.19 -0.15 -3 -3	NS NS NS NS NS 0.002 NS NS	0.33 0.28 0.26 0.21 0.54 - 0.21 0.49
[83] Pre-post 16 Fair	13	BWSTT 52 weeks 3 sessions/week Minimal load and max speed without knee buckling, losing proper weight shifting, and upright torso Up to 3 x 5-15 min bouts	Fat Mass (kg)	23.6 \pm 11.0	+0.4	NS	0.04
[84] Pre-post 16 Fair	5	Robotic Exoskeleton Walking 60-70% HRR 6 weeks 3 sessions/week Up to 60 mins	Body Mass (kg) BMI (kg/m²) BF (%)	79.7 \pm 12.5 24.5 \pm 1.7 35.4 \pm 7.1	+2.0 +0.6 -1.3	0.04 0.04 0.04	0.15 0.32 0.23
[85] Pre-post 15 Fair	9	BWSTT 26 weeks 3 sessions/week Intensity NR Until self-reported fatigue	TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) TC: HDL	1.51 \pm 0.20 4.91 \pm 0.19 1.29 \pm 0.19 3.25 \pm 0.22 3.83 \pm 0.33	-0.19 -0.55 +0.14 -0.42 -0.76	0.17 0.02 0.19 0.05 0.04	0.33 1.15 0.20 0.54 0.95
[86] Pre-post 14 Fair	9	BWSTT 24 weeks 3 sessions/week Based on self-reported fatigue Until self-reported fatigue	Glucose OGTT (AUC) Insulin OGTT (AUC)	- -	-15% -33%	<0.05 <0.05	- -
[87] Pre-post 13 Low	16	FES-walking 11 weeks 3 sessions/week Comfortable intensity Up to 3 sets	Body Mass (kg)	66.0	+1.3	0.06	-

BSWTT body-weight supported treadmill training, HRR heart rate reserve, AUC area under the curve † True study design is RCT, presented as pre-post due to two different exercise modalities being tested. *Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study designs.

Table 9. Overview of other exercise studies included in review but not grouped for qualitative analysis.

Study Design D&B Quality	n	Intervention	CMS Outcome	Group Baseline <i>Intervention (Control)</i> Mean ± SD	Change <i>Intervention (Control)</i>	p value*	ES
[88] RCT 19 High	48	Lower body RT and BSWTT or FES 24 weeks 3 sessions Intensity NR Up to 180 mins	Body Mass (kg) BMI (kg/m²) QUICKI	89.4 ± 20.3 (75.7 ± 21.0) 27.1 ± 6.4 (24.8 ± 6.6) 0.35 ± 0.04 (0.38 ± 0.06)	-0.20 (+5.03) 0.0 (+0.7) -0.002 (-0.012)	0.31 0.29 0.92	0.45 0.41 0.06
[89] Pre-post† 18 Fair	6	Combined RT, ACE, and FES 8 weeks 3 sessions/week ACE: 80-90% $\dot{V}O_{2PEAK}$, 15 x 1 mins Upper-body RT: 3 x 12 FES-knee extensions: 40 reps, increased by ~0.5-1 kg every 2 weeks	Body Mass (kg) Fat Mass (kg) Android Fat Mass (kg) TG (mmol/L) TC (mmol/L) HDL-C (mmol/L) LDL-C (mmol/L) Fasting Glucose (mmol/L) Fasting Insulin (pmol/L) Glucose OGTT (AUC) Insulin OGTT (AUC) HOMA-IR ISI-Matsuda IL-6 (pg/mL) TNF-α (pg/mL)	87.7 ± 15.0 - - 1.36 ± 0.66 4.44 ± 0.99 1.09 ± 0.16 2.73 ± 0.80 6.12 ± 1.14 115.3 ± 127.1 - - 4.6 ± 5.1 3.3 ± 2.0 1.7 ± 1.0 2.2 ± 0.4	↔ ↔ ↔ +0.39 -0.21 -0.05 -0.34 -0.54 -25.7 +4% -27% -1.3 +1.3 -0.7 -0.8	NS NS NS 0.47 0.94 0.96 0.75 0.04 0.91 0.87 0.34 0.83 0.98 0.20 0.27	- - - 0.45 0.25 0.27 0.48 0.56 0.24 0.14 0.28 0.31 0.43 0.95 0.97

†True study design is RCT, presented as pre-post due to two different exercise modalities being tested
 *Group x time interaction for RCT and non-randomised controlled trial, or pre-post change for pre-post study design

Table 10. Participant characteristics, statistical power, and control group (if applicable) of included studies.

Study	Control Type	Statistical Power	N (M/F)	Age (y)	TSI (y)	LOI	ASIA
[32]	General Exercises	NR	33 (29/4)	I:33 (15-42), C:37 (19-62)	I: 1.3 (0.2-12), C: 1.3 (0.3-10)	C7-L3	A-D
[48]	N/A	NR	10 (9/1)	39±10 (26-55)	9±9 (1-21)	C4-T11	A-C
[25]	N/A	No	19 (18/1)	Hybrid: 49±3 (31-64), Hand cycle: 47±3 (30-63)	Hybrid: 21±3 (13-34), Hand cycle: 16±2 (9-21)	C2-L2	A-D
[28]	N/A	NR	10 (8/2)	37±13 (23-55)	12±14 (1-34)	C7-T5	A-B
[62]	N/A	NR	5 (4/1)	31-50	3-25	C5-T8	A
[45]	N/A	NR	16 (16/0)	45±12	12±10	Thoracic	A-C
[39]	No exercise intervention	NR	14 (14/0)	I: 30±3, C: 29±3	I: 19±3, C: 9±3	NR	NR
[42]	Instructed to maintain PA levels	NR	23 (21/2)	I: 39±11, C: 42±13	I: 15±10, C: 9±10	C1-T11	A-D
[81]	N/A	NR	8 (6/2)	28±5 (20-34)	10±8 (2-24)	C4-C5	B-C
[80]	N/A	NR	6 (4/2)	38±15	8±9	C4-T12	A-B
[53]	N/A	NR	13 (12/1)	31±5 (21-41)	8±4 (3-16)	C4-T10	A-D
[37]	N/A	NR	9 (NR)	35±11 (25-50)	12±5 (5-18)	C5-T4	NR
[51]	N/A	NR	9 (9/0)	39±11 (28-44)	11±10 (1-27)	C5-T8	A-C
[41]	N/A	NR	34 (26/8)	FES: 57±14, RT: 54±17	FES: 9±10, RT: 10±11	C2-T12	C-D
[83]	N/A	NR	14 (11/3)	29±8 (20-53)	8±7 (1-24)	C4-T12	NR
[63]	Testosterone replacement therapy only	Yes	22 (22/0)	I: 37±12, C: 35±8	I: 10±9; C: 7±6	C5-T11	A-B (ISNCSCI)
[31]	N/A	NR	9 (9/0)	ACE: 41±13 (30-61); FES-Cycling: 37±7 (29-45)	ACE: 11±9 (2-26); FES-Cycling: 7±5 (4-14)	C8-T10	A-B
[64]	Standardised diet with no exercise intervention	NR	9 (9/0)	35±9 (21-47)	13±9 (2-26)	C5-T11	A-B
[79]	Stretching (3 days/week for 20-25 mins)	NR	18 (NR)	I: 52±12 (28-66), C: 52±15 (30-72)	NR	NR	C-D
[54]	N/A	NR	18 (13/5)	40±2 (25-57)	11±3	C4-T7	NR
[29]	N/A	NR	5 (5/0)	40±7	13.9±5.0	C4-L1	A-D
[78]	N/A	NR	8 (NR)	NR	NR	NR	NR
[46]	No exercise intervention	NR	34 (NR)	I: 37±11 (19-65); C: 43±9 (29-63)	I: 8±6 (1-22); C: 12±7 (3-24)	C4-S1	A-D
[56]	N/A	NR	5 (5/0)	35±3 (28-44)	10±3 (4-23)	C5-C7	A-B
[58]	N/A	NR	5 (5/0)	35±3 (28-44)	10±3 (4-23)	C5-C7	A-B
[40]	N/A	NR	11 (6/5)	31±4 (23-36)	12±7 (2-19)	C5-T9	NR
[34]	N/A	NR	9 (9/0)	38±10	16±7	T8-L1	A-B
[77]	N/A	NR	6 (6/0)	46±5 (24-56)	NR	T4-T10	A-B
[50]	N/A	NR	7 (5/2)	45±8 (30-53)	20±14 (3-40)	C5-T10	NR
[88]	No exercise intervention	Yes	48 (30/11)	I: 42±13; C: 34±12	I: 7±10; C: 6±7	NR	C-D
[57]	N/A	NR	12 (NR)	NR	>1	C4-C8 and T1-T10	NR

[84]	N/A	NR	5 (4/1)	60±6	8±5	C7-T10	NR
[33]	No exercise intervention	NR	15 (9/6)	33±6 (22-46)	7±4 (2-16)	C5-T11	A-B
[44]	Standard Care	NR	17 (11/6)	37±7 (23-53)	10±7 (2-27)	C4-L1	A-C
[73]	N/A	NR	12 (10/2)	36±12 (16-45)	11±6 (5-24)	C6-L1	A-C
[87]	N/A	NR	16 (13/3)	28±7 (21-45)	4±3 (0.7-9)	T4-T11	NR
[59]	N/A	NR	8 (8/0)	39±3	>4	C5-T11	A-B
[52]	N/A	NR	18 (16/2)	40±11 (26-61)	3±2 (1-9)	C3-L1	B-D
[89]	N/A	NR	6 (6/0)	50±8 (36-58)	24±8 (10-30)	C6-T6	A-B
[70]	N/A	NR	5 (5/0)	36±5	13±7	C5-T10	A
[30]	N/A	NR	14 (NR)	Supine: 34±12; Sitting: 33±7	Supine: 9±13; Sitting: 14±6	CT-T1	NR
[35]	N/A	NR	12 (11/1) (2 non-SCI)	38±10 (22-58)	15±7 (4-29)	C6-L3	NR
[43]	No exercise intervention	NR	20 (20/0)	I: 25±3; C: 26±3	I: 10±4; C: 9±4	T9-T12	A
[60]	N/A	NR	10 (8/2)	35 (27-45)	12 (3-23)	C6 and T4	NR
[36]	N/A	NR	12 (12/0)	31±9 (19-45)	2±1 (1-3)	<T10	NR
[47]	N/A	NR	5 (5/0)	38±4 (34-43)	5±1 (1-7)	T6-T12	NR
[26]	No exercise intervention	Yes	21 (15/6)	I: 46±6, C: 48±10	I: 20±10; C: 14±11	T4-L3	A-D
[71]	N/A	NR	4 (4/0)	20-35	4±3 (1-8)	T4-T6	NR
[86]	N/A	NR	9 (8/1)	31±3	8±3	C4-T12	C
[69]	N/A	NR	11 (7/4)	29±15 (18-54)	6±3 (0.5-11)	C4-T6	NR
[68]	N/A	NR	19 (16/3)	19-47	2-17	C4-T10	NR
[55]	N/A	NR	8 (7/1)	32±2 (23-41)	12±2 (5-24)	C7-L1	NR
[65]	N/A	No	12 (9/3)	38±13 (19-63)	6±6 (1-17)	C4-T10	NR
[27]	No exercise intervention	NR	17 (17/0)	30±4 (I & C)	5±0	≤T5	NR
[66]	N/A	No	14 (11/3)	27±5 (28-57)	8±7 (2-22)	C4-T7	A-B
[49]	Standard Care	NR	45 (38/7)	I: 37±12; C: 35±12	I: 8 (1.5-43), C: 6 (1-27)	C1-L5	A-C
[74]	N/A	Yes	12 (11/1)	33±4 (22-60)	8±3 (0-33)	C4-T2	NR
[61]	No exercise intervention	NR	15 (15/0)	33 (21-48)	9 (1-21)	NR	A-B
[85]	N/A	NR	9 (8/1)	31±3	8±3	C4-T12	C
[67]	N/A	NR	5 (5/0)	36±5	13±7	C5-T10	A
[72]	N/A	NR	9 (8/1)	39±3 (25-52)	11±3 (1-25)	C5-T12	A, C
[75]	N/A	NR	10 (9/1)	39±9 (23-53)	11±6 (1-20)	T1-T12	A, C
[82]	N/A	NR	14 (10/4)	51±17	2-10	NR	Motor Incomplete
[76]	N/A	NR	10 (8/2)	47±18	18±14 (2-39)	T4-T12	A-C
[38]	N/A	NR	11 (11/0)	31±8 (20-49)	2±1 (0.5-4)	T8-T12	A

TSI time since injury, LOI level of injury, ASIA American Spinal Injury Association Impairment Scale, NR not reported, ISNCSCI International Standards for Neurological Classification of Spinal Cord Injury, ROM range of motion; I Intervention, C Control.



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Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title Page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplement 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6



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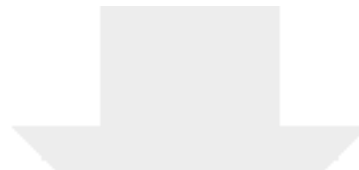
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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 3-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables 3-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3-10
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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